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The role of circulating free nucleic acids on Alzheimer's Disease

O papel dos ácidos nucleicos livres circulantes na Doença de Alzheimer

El papel de los ácidos nucleicos libres circulantes en la Enfermedad de Alzheimer

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Abstract

The study aims to understand the multifactorial foundation that could contribute to a deeper understanding of this issue. Alzheimer's disease is a neurodegenerative disorder primarily caused by idiopathic factors. However, it is almost universally agreed that genetic factors and the deposition of beta-amyloid plaques in senile plaques, along with tau protein, negatively influence its progression. Additionally, more recent evidence suggests a greater plausibility of factors that have been less discussed until now, such as circulating free nucleic acids. Oxidative stress caused by a neuroinflammatory process is triggered by the recognition of these substances in their circulating form, resulting from tissue damage caused by free radicals, which appear as damage-associated molecular patterns (DAMPs). This occurs through a positive feedback process involving the activation of the innate immune system, including microglia, astrocytes, blood-brain barrier proteins, cytokines, the complement system, and transmembrane receptors. In an insufficient attempt to clear the nervous system of DAMPs, this response ultimately induces and sustains a chronic

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immune cascade. However, despite the strong relationship between these factors and the development of Alzheimer's disease, the topic remains recent and clinically underexplored. Therefore, further theoretical exploration and the development of more laboratory tests are necessary to substantiate the theoretical framework discussed in the current literature on this subject.
Keywords: Alzheimer's disease; Neuroinflammation; Oxidative stress; DAMPs; Circulating free nucleic acids.

Resumo

O estudo tem como objetivo compreender a base multifatorial que pode contribuir para uma compreensão mais profunda dessa questão. A doença de Alzheimer é um distúrbio neurodegenerativo causado principalmente por fatores idiopáticos. No entanto, é amplamente aceito que fatores genéticos e a deposição de placas beta-amiloides, juntamente com a proteína tau, influenciam negativamente sua progressão. Evidências mais recentes sugerem ainda a plausibilidade de outros fatores menos discutidos até o momento, como os ácidos nucleicos livres circulantes. O estresse oxidativo causado por um processo neuroinflamatório é desencadeado pelo reconhecimento dessas substâncias em sua forma circulante, resultante de danos teciduais causados por radicais livres, que aparecem como padrões moleculares associados a danos (DAMPs). Esse processo ocorre por meio de um ciclo de retroalimentação positiva envolvendo a ativação do sistema imune inato, incluindo micróglias, astrócitos, proteínas da barreira hematoencefálica, citocinas, sistema complemento e receptores transmembrana. Na tentativa insuficiente de eliminar os DAMPs do sistema nervoso, essa resposta acaba induzindo e sustentando uma cascata imunológica crônica. Apesar da forte relação entre esses fatores e o desenvolvimento da doença de Alzheimer, o tema ainda é recente e pouco explorado clinicamente. Portanto, são necessários mais estudos teóricos e laboratoriais para fundamentar o arcabouço teórico discutido na literatura atual sobre o tema.
Palavras-chave: Doença de Alzheimer; Neuroinflamação; Estresse oxidativo; DAMPs; Ácidos nucleicos livres circulantes.

Resumen

El estudio tiene como objetivo comprender la base multifactorial que podría contribuir a una comprensión más profunda de esta cuestión. La enfermedad de Alzheimer es un trastorno neurodegenerativo causado principalmente por factores idiopáticos. Sin embargo, se acepta ampliamente que los factores genéticos y la deposición de placas beta-amiloides, junto con la proteína tau, influyen negativamente en su progresión. Además, evidencias más recientes sugieren una mayor plausibilidad de factores que hasta ahora han sido poco discutidos, como los ácidos nucleicos libres circulantes. El estrés oxidativo causado por un proceso neuroinflamatorio se desencadena por el reconocimiento de estas sustancias en su forma circulante, resultante del daño tisular causado por radicales libres, que aparecen como patrones moleculares asociados al daño (DAMPs). Este proceso ocurre mediante un ciclo de retroalimentación positiva que involucra la activación del sistema inmunitario innato, incluidas la microglía, los astrocitos, las proteínas de la barrera hematoencefálica, las citocinas, el sistema del complemento y los receptores transmembrana. En un intento insuficiente por eliminar los DAMPs del sistema nervioso, esta respuesta termina induciendo y manteniendo una cascada inmunológica crónica. A pesar de la fuerte relación entre estos factores y el desarrollo de la enfermedad de Alzheimer, el tema sigue siendo reciente y poco explorado clínicamente. Por lo tanto, se necesitan más estudios teóricos y de laboratorio para fundamentar el marco teórico discutido en la literatura actual sobre este tema.
Palabras clave: Enfermedad de Alzheimer; Neuroinflamación; Estrés oxidativo; DAMPs; Ácidos nucleicos libres circulantes.

1. Introduction

Currently, it is widely accepted that the pathophysiology of Alzheimer’s disease is based on the deposition of beta-amyloid plaques and phosphorylated tau protein aggregates in the central nervous system. The presence of these compounds in biological samples has been used as biomarkers in the preclinical stages of the disease. It is also known that there is a strong connection with genetic factors, advanced age, and sex, with the disease being more prevalent in women. Additionally, neuroinflammation, glial cell dysfunction, and vascular changes are also associated factors.

For a long time, it was believed that endogenous genetic material had no pathological potential; however, recent research indicates that not only can it be recognized as an antigen, but it is also closely related to the disease (Sanders, 2023). This topic has gained traction within the scientific community, primarily as biomarkers secondary to other processes, but not as pathogens directly involved in the disease's development.

Based on this, a hypothesis was raised that circulating cell-free nucleic acids (cfDNA) are direct causes of the inflammatory process in Alzheimer's disease. Given the obscurity of this factor, the present study aimed to explore the pathophysiological mechanisms, which have been relatively unexplored or neglected, responsible for the neuroinflammation caused by circulating cell-free nucleic acids in Alzheimer's disease. The study seeks to establish a link between oxidative stress-induced damage and disease progression alongside already established mechanisms, highlighting the role of circulating species beyond mere biomarkers.

The goal is to clearly and integratively present, using previously isolated information, the new factors that have proven to be relevant in the course of Alzheimer's disease. The study aims to understand the multifactorial foundation that could contribute to a deeper understanding of this issue.

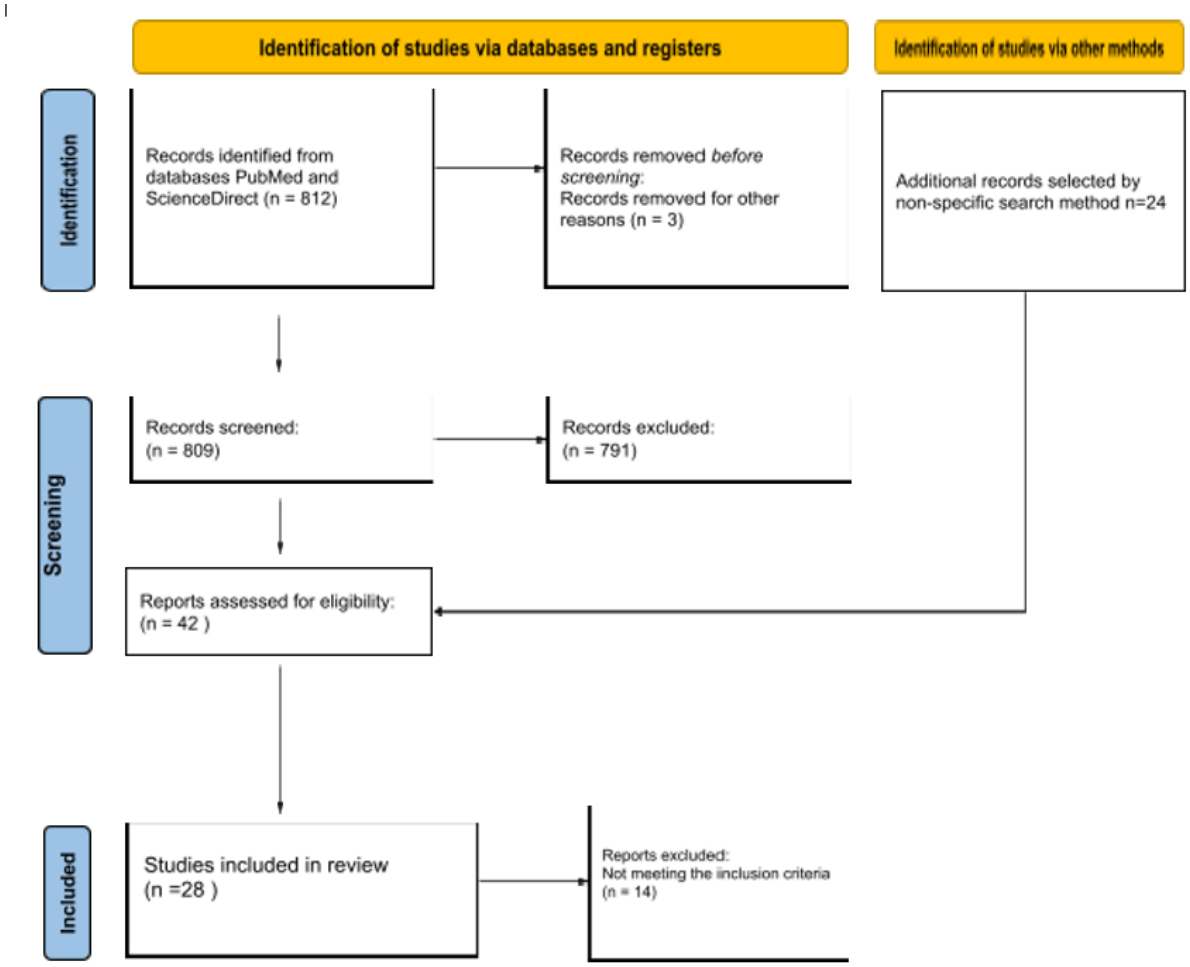
2. Methodology

This is a systematic review, conducted in May 2024. A search was performed in the PubMed and ScienceDirect databases using the Health Sciences Descriptors (DeCS) "Alzheimer" AND "circulating free nucleic acids," "Nucleic acids" AND "Alzheimer," resulting in 136 articles. From these, 12 were selected for full-text reading based on the title and abstract relevance to the topic. No articles were excluded after full-text review. The inclusion criteria were systematic reviews, meta-analyses, or clinical trials, written in English or Portuguese. Exclusion criteria included duplicate articles, those with little or no relation to Alzheimer's disease, or those not meeting the established criteria.

For the analysis of clinical results, the terms "Nucleic acids" AND "Alzheimer" AND "Case-control" were used in the PubMed and ScienceDirect database, yielding 676 articles, of which 6 were selected for full-text reading based on their relevance to the topic and the following inclusion criteria: full-text availability, clinical trial articles, and randomized clinical trials, in Portuguese or English, published in the last 10 years. Only articles specifically addressing Alzheimer's disease, without interference from other conditions, were selected. Their results were compared to identify the presence and the consequent relationship of circulating nucleic acids with the development of Alzheimer's disease.

Additionally, three other subcategories with a strong connection to the theme were delineated: chronic neuroinflammation, innate immune response, and emerging factors in Alzheimer's disease research. Based on this, complementary literature was selectively included as needed throughout the research, using the PubMed database. Consequently, 24 supplementary articles were selected, with 3 articles later eliminated after full-text reading.

Figure 1 - Flow diagram.



Source: Authors.

Table 1 - Clinical results.

Study	Study design	Sample size	Method	Results
Kenny, 2019	Case-control	9 people with Alzheimer Disease 15 controls	Identification of miRNA through qPCR in Tears	Increase in miRNA Concentration in the Alzheimer Disease Group (P<0.05)
Liu, 2021	Case-control	92 people with Alzheimer Disease 30 controls	Analysis of Serum miRNA through qPCR	Elevated Exosomal miRNA in Serum and Cerebrospinal Fluid of Alzheimer Disease Patients (P<0.05)
Kenny, 2019	Case-control and longitudinal cohort	25 people with Alzheimer Disease 31 controls	Analysis of Serum miRNA through RT-qPCR	Significant Increase in miRNA Concentration between Control and Alzheimer Disease Groups (p=0.0168)
Bautista, 2019	Case-control	53 people with Alzheimer Disease 27 controls	Analysis of Oxidized DNA in Urine through Mass Spectrometry and Chromatography	Increase in Concentration of Two Hydroxylated Guanosine-Derived DNA Species (p=0.019) and Low Statistical Relevance in Other Species

Derkow, 2018	Case-control	19 people with Alzheimer Disease 10 controls	Analysis of miRNA Presence in Cerebrospinal Fluid using PCR	Species of the let-7 Family Showed High Concentration in Alzheimer Disease ($p<0.05$). Their Neurotoxicity Was Observed
García, 2023	Case-control	67 people with Alzheimer Disease , 47 controls	Analysis of miRNA in Plasma using an Automated Program	Increase in miRNA Concentration Induces Inflammatory Processes

Source: Authors.

3. Results

A new approach to pathophysiology

A positive feedback loop of chronic inflammatory action in the central nervous system was identified, involving tissue damage and death, the release of genetic material fragments, and an immune response. Based on cellular death, Sanders (2023) suggests that circulating free nucleic acids (cfDNA) have the ability to cause damage to neural tissue, independent of other factors such as beta-amyloid plaques, tau protein, and other elements. In his work, he states that part of the genetic material is released due to cell membrane rupture, aiming to signal to other cells the damage incurred, in the form of exosomes, which are primarily identified through PRR receptors, in the form of Pathogen Associated Molecular Patterns (PAMPs), inducing a response similar to virus-induced inflammation, with increased immune activity, notably microglia, and elevated levels of NF-kB, Interferon, cytokines, interleukins, and chemokines, resulting in oxidative damage or apoptosis, considering that elevated levels of NF activate caspases, enzymes involved in programmed cell death2. In addition to the excess of certain genetic material fragments, the lack of some, such as miR 137 cKO, identified in Li's (2024) work, can also induce the release of these substances3. However, a systematic review conducted by Van den Berg (2020) found that the sub-expression of free nucleic acids is predominant, although their increase also influences neuroinflammation4. Another study (Burgos, 2014) indicated that both factors play a role in this process.

Free miRNAs influence the expression of other genes, such as amyloid precursor enzyme (APP), APP-cleaving enzyme, among others, while miRNAs in vesicles can be phagocytosed or end up inducing the release of chemokines and other inflammation-indicating substances. In other words, the impact that circulating nucleic acids have depends on how they were released into the extracellular fluid.

Hanisch (2002) demonstrates in his study, based on in vivo and in vitro experiments, that microglia are capable of synthesizing a significant amount of these substances in response to immune stress, further supporting the possibility that microglia are a primary and independent source of signaling. He also notes the production of reactive oxygen species as a consequence. The oligomerization of exosomes with these substances and cells, and the subsequent formation of inflammasomes, results in the generation of reactive species of oxidatively damaged nucleic acids, which were experimentally identified in greater amounts in the brain with AD, and also have a cumulative effect, leading to cytotoxicity and synaptotoxicity6. Additionally, Tsuji (2021) identifies TLR9 receptors as one of the main factors in the recognition of cfDNA and the trigger for cytokine production, and associates PRR receptors with PAMPs. He also emphasizes the presence of circulating free nucleic acids, in the form of nucleosomes and neutrophil extracellular traps (NETs), as well as exosomes, noting that nucleosomes need to bind to TLR2 and RAGE receptors to result in neuroinflammation. No distinction in reactivity between nucleosomes and exosomes was identified. It was also found that mitochondrial DNA, single-stranded DNA, and DNA fragments are the only types identified by the organism. Regarding RNA, the only one whose relationship was identified was mitochondrial RNA.

Small amounts can be tolerated, and large fragments of DNA, double-stranded DNA, or methylated single-stranded DNA are digested by lysosomes, under the action of the endonuclease DNase II. However, other types of DNA have demonstrated the ability to evade this system of degradation of circulating genetic material due to lower affinity for receptors, at least when above the threshold of tolerance for this system. Tsuji (2021) also points out that cfDNA bound to histones becomes immune to DNase. Binding to TLR9 induces an inflammatory cascade that results in apoptosis, which in turn activates microglia, identified as the primary signaling cell in the CNS, responsible for maintaining a chronic response due to failure in clearing dead cells and amyloid beta plaques, albeit to a lesser extent. Despite its prominence in AD pathology, in the early stages of the disease, microglia are effective in removing amyloid plaques, suggesting that the deposition of AB is not the initial trigger of the disease. Thus, it is hypothesized that its hyperexpression, caused by the recognition of cfDNA and cellular aging, are factors leading to the inflammatory condition, even before the exacerbation of senile plaques.

It was also discovered that not only cfDNA from nervous tissue and bone marrow has the potential to present as an antigen. Ectopic cfDNA also demonstrated pathological potential, thus numerous indirect relationships of tissue damage with AD emerged. Through laboratory tests, it was found that renal problems can hinder the elimination of some nucleic acids, as some are excreted in the urine, as well as the binding of cfDNA to the Amyloid P peptide, which protects them from DNases and makes them soluble in plasma, allowing their circulation through body compartments. Concerning the brain, the blood-brain barrier exerts a protective effect; however, when damaged by inflammatory processes and oxidative stress-related free radical damage, it may allow the passage of harmful substances, in this case, cfDNA. Additionally, it is responsible for modulating microglial action through the control of signaling molecule passage. Thus, failure of this mechanism favors microglial overexpression, suggesting an increase in the intensity of the immune response in the AD-affected organism.

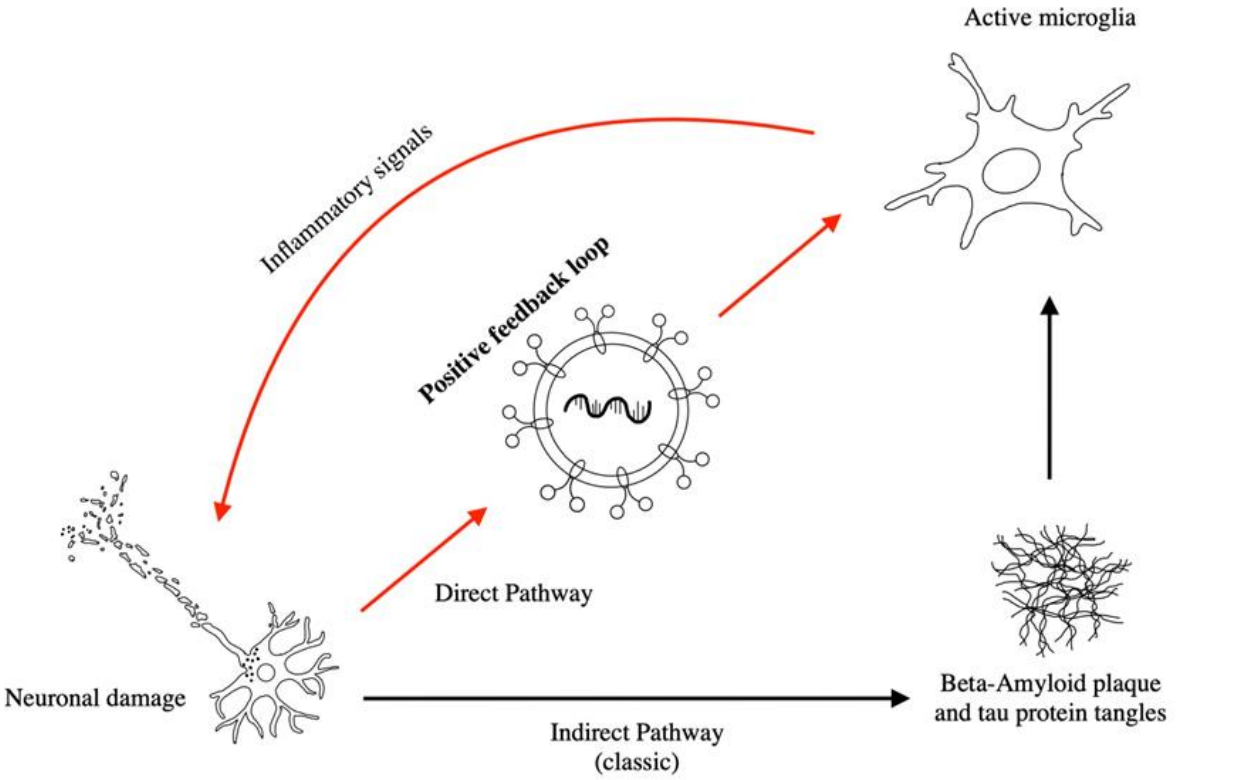
Recent evidence has detected Aβ as part of the innate immune response, suggesting that the deposition of this peptide is secondary to an ongoing infection in the individual's body, potentially related to oxidative stress resulting from chronic neuroinflammation caused by cfDNAs, mtDNA, mtRNA, and nucleosomes. Prokop (2013) also states that AB deposition is not an appropriate signaling mechanism for microglia.

A recent study examined the mechanisms of cell death and how each can impact neuroinflammation. In line with previous discussions, it was found that necroptosis can be activated by PRRs TLR3 and TLR4, which have already been indicated as the main receptors of cfDNA, along with TLR9. Additionally, pyroptosis can occur due to lysosomal stress resulting from cellular digestion by free radicals and reactive oxygen species, leading to the formation of inflammasomes and membrane pores, which can not only cause cell death but also allow the release of contents, particularly nucleic acids. In the brain, microglia are the primary responders to inflammasomes, supporting their direct involvement in triggering inflammatory signals in late-stage AD, given that their role is beneficial in the initial clearance of apoptotic bodies, lysosomes, and other cell death corpuscles, as well as amyloid beta plaques. Apoptosis can occur in smaller quantities, especially mediated by caspase 1, which is not typically associated with immunogenic responses but has recently gained visibility due to evidence of its involvement in these conditions (Murao, 2021). Finally, Mangalmurti (2022) found that cell death with membrane rupture or increased permeability is directly related to the release of pro-inflammatory factors that lead to a chronic state of neuroinflammation.

Yang (2020) highlights the synergistic relationship between the complement system and innate immunity in the exacerbation of AD due to their mutual activation in response to a pathogen. It was found that increased levels of certain complement factors, particularly C1q, are associated with increased glial activation, while its deficiency was linked to less synaptic decline. Therefore, this co-activation with TLR receptors, NF-kB, and interleukins, as well as participation in inflammasome formation, denotes a significant relationship of this system with the main inflammatory mechanisms of the

disease. In agreement, Shah (2021) notes that the complement system is prioritized by the blood-brain barrier, which facilitates the passage of signaling factors through it, promoting the inflammatory state; thus, its damage can interfere with this important defensive system. Additionally, astrocytes can also influence this condition in another way: by altering their conformation in response to CNS damage, becoming active and assisting in the clearance of amyloid beta plaques and other harmful substances, albeit insufficiently, thereby creating a chronic positive feedback inflammatory condition similar to microglia.

Figure 2 - Simplified schematic of the neuroinflammation pathways in Alzheimer's disease.



Source: Authors.

Direct pathway: Exosome (or other types of extracellular vesicles) containing genetic material fragment recognized as an antigen. Indirect pathway: Free miRNA influences the gene expression of other factors related to Alzheimer's disease, such as Substance PPA, for example. It is evident that within the classical Alzheimer's pathway, there is a secondary pathway (in red) that induces the inflammatory process more rapidly.

Hematoencephalic barrier

Regarding microglia exposure to antigens, astrocytes are primarily responsible for increasing the permeability of the blood-brain barrier to antigens and hindering the secretion of toxic substances. Their dysfunction results from damage caused by reactive oxygen species and cytokines, and glutamate, all of which are neurotoxic and produced by oxidative stress from microglia. Even when undamaged, it has been found that astrocytes allow the passage of miRNA mediated by exosomes; thus, antigens pass through their membrane one way or another. Additionally, beta-amyloid has also demonstrated harmful potential to the blood-brain barrier (BBB), as angiograms have revealed its deposition in the endothelium and a consequent increase in permeability to water and other small substances, such as tau protein and AB. This supports the hypothesis of a secondary role

of AB in the development of Alzheimer's disease, knowing that its action on the BBB acts as a trigger for a future, more powerful inflammatory process driven by other substances. This preference for smaller molecules aligns with the observed higher prevalence of smaller nucleic acid fragments in inflammation; however, this has not been experimentally verified, as the study in question relied on the classical Alzheimer's model, considering only substances already accepted in the scientific community as causes of the disease. Therefore, future investigation into the permeability of the brain endothelial cells to free DNA and RNA species is necessary.

Experimental results

Although most studies lack experimentation, some have shown promising results, albeit scarce. Elevated levels of genetic material, especially RNAs, have been found in high quantities in various bodily fluids of individuals with Alzheimer's disease, indicating a possible relationship between elevated levels of such substances and the development of the pathology.

Kenny (2019), through the analysis of tear content from a case-control group using PCR, discovered that small RNA fragments, between 10 and 40 nucleotides, are approximately twice as concentrated in the AD subgroup compared to the control group. Contrary to other studies, it was found that the size of the molecule is the primary factor rather than a specific class of genetic material. Additionally, in line with the hypotheses raised in this work, it was found that most genes originate from the cytoplasm or are secreted in the form of exosomes in response to cellular damage. In another study, Kenny analyzed human blood samples, seeking small RNA fragments again using PCR. This time, a specific species (miR-206) was noted, which showed significant elevation in samples from AD patients.

Another study quantitatively analyzed microRNA concentration in a human case-control group with AD patients, using blood samples and analyzing the extracted serum. The PCR technique was used to trace specific miRNA species (miR-193b), also manifested in the form of exosomes, similar to Kenny's study. Additionally, in rats, this material was also found in cerebrospinal fluid (CSF) as well as in serum.

Bautista (2019), on the other hand, explored a possible pathophysiological mechanism beyond simple genetic material quantification. A strong relationship was demonstrated between oxidative DNA damage and neuroinflammation, due to a lack of antioxidants and high oxygen metabolism in nervous tissue. It was found that the hydroxylation of guanosine-derived compounds (8-OHdG) is one of the most important biomarkers of DNA damage, being statistically significant among oxidatively damaged species. For identification, urine samples from patients with early-stage AD were analyzed using mass spectrometry and chromatography. The oxidation of other nucleotides, such as those derived from tyrosine, did not show statistical differences.

Derkow (2018) analyzed the CSF of human AD patients using PCR. In this study, extracellular vesicles containing genetic material, also derived from neurodegeneration through lysosomes and interaction with TLR7 receptors, were identified. The species analyzed included the let-7 miRNA family, with let-7b and let-7e being significantly elevated in AD patients. In another phase of the study, the neurotoxicity of these compounds was confirmed in vitro. The choice of this material was due to its stability in CSF, allowing its tracking in both short and long-term studies. Therefore, its presence could also be an important biomarker.

García (2023) found elevated miRNA levels in patients as a consequence of beta-amyloid deposition and cellular damage. A machine learning model was developed to identify RNA fragments related to pathophysiological processes caused by Alzheimer's disease damage. This model was applied to a case-control group of 114 people, comprising 67 AD patients and 47 controls. While neurotoxicity was not directly studied, as the study emphasized the use of genetic material as a biomarker rather than a pathogen, an increase in genes related to cell death, apoptosis, immune signaling, and lysosomal degradation was

observed. This suggests their involvement in the processes mentioned in this text, but it is unclear whether their involvement is direct, through accumulation in the nervous system and recognition as an antigen, or if they are simply markers of other processes. This study also points out BBB fragility as a potential risk factor for the disease.

In the most recent study (Burgos, 2014), four species of microRNA with high relevance were identified: miRNA-9, which showed a decrease in AD patients; miR-34c, which, when present in large quantities, accumulates in the hippocampus of people with the disease and negatively influences memory; miR-101, which appeared as a biomarker due to its lower quantity in AD, increasing neurofibrillary plaque formation by failing to regulate substances like APP; and the negative expression of miR-132, which was associated with neuronal dysfunction in patients with this condition. The primary pathway was not considered in this study, but the hypothesis was raised.

4. Discussion

Despite numerous studies supporting the possibility that free nucleic acids influence the development of Alzheimer's disease and neurodegeneration through the activation of the immune system, it is important to note that not all species of these radicals are harmful when present in large quantities. On the contrary, recent studies have confirmed that the lack of specific types of microRNA can have negative effects on microglial regulation, increasing its expression in the active form and promoting the inflammatory process. Additionally, free species may not have a direct relationship with the activation of defense mechanisms, acting merely as biomarkers released through cellular content release caused by other mechanisms, whether due to AB deposition or idiopathic causes. Thus, further studies are needed to identify the nucleotides and their derivatives capable of inducing this response. Currently, few studies have focused on deciphering which groups exhibit the greatest prevalence of cfDNA, miRNA, and extracellular vesicles. Therefore, more epigenetic studies and factors such as age, sex, race, and others are necessary to precisely determine which risk factors influence this issue.

The role of DNA has been underexplored, with most studies focusing on microRNAs. Thus, new research involving cfDNA is necessary. cfDNA represents a complex network of signaling with both direct and indirect causes. The proposition of this theory does not negate previous theories, as they are, in fact, interrelated. Exploring cfDNA can offer additional insights into the mechanisms of Alzheimer's disease and neurodegeneration, complementing existing research on microRNAs and providing a more comprehensive understanding of the disease's pathology.

5. Conclusion

In total, biological samples from 668 individuals were analyzed. Most studies associate increased levels of nucleic acids with inflammation. However, other studies found the opposite effect, where elevated levels of nucleic acids exhibited a protective role. Additionally, some studies did not identify a clear relationship between these factors. These diverse findings highlight the complexity of nucleic acid roles in biological processes and suggest that their effects may be context-dependent. Further research is needed to clarify these inconsistencies and to better understand the conditions under which nucleic acids may exert protective versus detrimental effects.

Contrary to expectations, there was insufficient evidence to position free nucleic acids as a primary factor in the development of Alzheimer's disease (AD). The amyloid theory remains predominant, although nucleic acids share similar pathophysiological features and exert significant influence through oxidative damage and the initiation of an inflammatory cascade. Despite this, some studies were unable to demonstrate a direct effect of genetic material on inflammation, identifying it only as intermediaries or consequences of other pathological processes. This underscores the need for further research to

elucidate the precise role of free nucleic acids in the context of AD and to determine how they interact with other known mechanisms of the disease.

Among the limitations of this article is the lack of long-term studies and patient follow-up. Due to this, analogies with traditional models were established in the absence of specific studies. However, future laboratory research is essential to experimentally validate the proposed hypotheses. Addressing these gaps will provide a more robust understanding of the role of free nucleic acids in Alzheimer's disease and help confirm their potential impact on disease mechanisms.

Furthermore, numerous mechanisms involved in the inflammatory process have been identified. Therefore, there is a need to precisely identify each of these mechanisms and other substances to assign them specific functions within this complex process. Understanding the distinct roles and interactions of these elements will be crucial for developing targeted therapeutic strategies and advancing our knowledge of the underlying pathology of Alzheimer's disease.

Conflicts of Interest

The authors declare no conflicts of interest.

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