ARTIGO DE REVISÃO

RELATION BETWEEN HYPOACUSIS AND ALZHEIMER'S DEVELOPMENT LATER IN LIFE: A NARRATIVE REVIEW

A relação entre hipocusia e desenvolvimento do Alzheimer mais tarde na vida: uma revisão narrativa

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ABSTRACT

This comprehensive study examines the intricate relationship between hearing loss, aging, and Alzheimer's disease. Three main mechanisms are explored: cognitive overload, sensory deprivation, and cognitive reserve reduction. The cognitive overload hypothesis suggests that individuals with hearing impairment allocate more cognitive resources to listening, potentially accelerating cognitive decline. The sensory deprivation mechanism proposes that hearing loss contributes to reduced cognitive stimulation, leading to brain atrophy and a decline in cognitive reserve, increasing dementia risk. The study critically analyzes existing research, challenging a straightforward causal link between Alzheimer's and hearing loss, considering confounding factors. It discusses conflicting evidence on the impact of hearing loss on cognitive reserve, emphasizing ongoing debates. The study reviews a prospective Australian cohort using hearing aids, reporting positive outcomes but acknowledging data limitations. In conclusion, it calls for nuanced understanding, recognizing the complexity of the relationship, and advocates for comprehensive randomized clinical trials, highlighting the ongoing ACHIEVE-P trial as a promising avenue for future research.

Keywords: Hypoacusis. Alzheimer. Hearing Loss.

RESUMO

Resumo: Este estudo abrangente examina a intricada relação entre perda auditiva, envelhecimento e doença de Alzheimer. Três mecanismos principais são explorados: sobrecarga cognitiva, privação sensorial e redução da reserva cognitiva. A hipótese da sobrecarga cognitiva sugere que indivíduos com deficiência auditiva alocam mais recursos cognitivos para ouvir, potencialmente acelerando o declínio cognitivo. O mecanismo de privação sensorial propõe que a perda auditiva contribua para uma redução na estimulação cognitiva, levando à atrofia cerebral e a um declínio na reserva cognitiva, aumentando o risco de demência. O estudo analisa criticamente a pesquisa existente, desafiando uma ligação causal direta entre Alzheimer e perda auditiva, considerando fatores de confusão. Discute evidências conflitantes sobre o impacto da perda auditiva na reserva cognitiva, enfatizando debates em curso. O estudo revisa uma coorte prospectiva australiana que usa aparelhos auditivos, relatando resultados positivos, mas reconhecendo limitações de dados. Em conclusão, ele pede uma compreensão matizada, reconhecendo a complexidade da relação, e defende ensaios clínicos randomizados abrangentes, destacando o ensaio ACHIEVE-P em curso como uma via promissora para pesquisas futuras.

Palavras-chave: Hipocusia. Alzheimer. Perda auditiva.

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INTRODUÇÃO

According to the World Health Organization (WHO), among dementia syndromes, Alzheimer's Disease (AD) is the most common cause of cognitive decline associated with aging, accounting for approximately 70% of all dementia cases. In this perspective, Alzheimer's Disease holds significant epidemiological relevance and a substantial social impact, as it is the primary cause of cognitive impairment after the age of 65. [1,3]

Alzheimer's Disease was first described in 1907 by neuropathologist Alois Alzheimer, who characterized it as a degenerative, progressive, and irreversible disorder of neuronal cells with insidious behavior, causing various impairments to cognitive ability. As the leading neurodegenerative pathology, one of the initial clinical symptoms is the loss of recent memory with preservation of remote memories. The disease can manifest in its early form (linked to genetic and familial factors, affecting 5% of Alzheimer's patients, with symptoms appearing around the age of 40) or in its late form (more common, sporadic in nature, and occurring after the age of 65). [1,14,17]

Regarding treatment, it is primarily palliative, aiming to slow down the disease progression and maintain the quality of life. Due to the limited efficacy of targeted pharmacotherapy (inhibiting cholinesterase enzymes to increase acetylcholine availability and divert from glutamate toxicity to neurons), dementia management also includes non-pharmacological treatment, involving activities that stimulate the preservation of cognitive reserve. [3] Additionally, an approach gaining prominence among researchers worldwide is the reduction of Alzheimer's Disease incidence through the identification and control of risk factors, proving to be a promising strategy for intercepting the disease. [3,17]

Currently, it is known that advanced age, positive family history, and biological inheritance are risk factors for Alzheimer's Disease, but these factors cannot be modified and, therefore, cannot prevent disease progression. However, evidence suggests that identifying other modifiable and potentially preventable risk factors can aid in Alzheimer's patient management. In this context, the Lancet Commission of 2020 reported that modifiable risk factors account for about 40% of dementia cases worldwide, emphasizing the importance of addressing avoidable risk factors for dementia prevention. [8,10]

In this perspective, approximately 40% of dementia cases could likely be prevented by addressing modifiable risk factors such as systemic arterial hypertension, obesity, diabetes, depression, sedentary lifestyle, smoking, social isolation, low formal education, excessive alcohol intake, traumatic brain injury, air pollution, and notably, hearing loss. [16] In this context, it is vital to focus on reducing modifiable risk factors through preventive measures; evidence shows that successful management of modifiable

risk factors can be effective in both delaying or preventing the disease and reducing healthcare costs. [4]

Active research in the literature has revealed significant advances in the search for modifiable risk factors. Epidemiological studies suggest an association between aging, Alzheimer's Disease, and hearing loss. This connection is based on the fact that two-thirds of adults over 70 years old have clinically significant hearing impairment that can affect daily communication and, consequently, cognitive reserve. [3]

Furthermore, relevant data include a 24% increase in the risk of cognitive impairment among individuals with hearing loss, resulting in accelerated cognitive decline and a higher risk of developing dementia. [2] Additionally, midlife hearing loss has been identified as responsible for 9% of dementia cases, indicating a significant (though potentially reversible) portion of the disease burden. (5,6) For these reasons, the question arises whether these cases could be detected early through auditory evaluation or prevented with hearing treatment and rehabilitation. Multicenter studies, such as Livingston et al., 2017, point towards defining hearing loss as a biomarker for cognitive impairment and dementia, becoming a potential and attractive target for Alzheimer's Disease prevention strategies. [2,3,4]

The objective of this literature review is to map the association between hearing loss and dementia and determine if there is a causal relationship between the two conditions in the literature. Additionally, it aims to emphasize the importance of addressing this finding appropriately and investigating common and causal mechanisms that may explain the nature of this relationship.

METHODS

The present study is a narrative literature review on hypertensive disorders during pregnancy and cognitive decline throughout life. The research was conducted using the DeCS/MeSH descriptors "Hypoacusis," "Hearing Loss," and "Alzheimer," combined with the boolean operators "AND" and "OR," for searching the electronic databases PubMed and ScienceDirect. Articles selected for review were English literature reviews published in the last 6 years (2017-2023). These articles were analyzed based on the year of publication, time frame, evaluation method, objectives, and main results. In total, 702 articles were identified, with 295 from PubMed and 407 from ScienceDirect. After applying inclusion criteria, 204 articles were ultimately analyzed, and 20 were selected for inclusion in this review.

RESULTS

The text discusses dementia as a slow and progressive reduction of mental functions leading to dysfunctions in memory, learning ability, psychological behavior, and other aspects. Alzheimer's Disease, a progressive and fatal

neurodegenerative disorder characterized by cognitive and memory deterioration, impairment of daily activities, and behavioral dysfunction, is the predominant type of dementia in society. Studies and findings related to this pathology are crucial for establishing new associations and risk factors, leading to the development of new perspectives on prevention, diagnosis, and treatment.

The potential relationship between the development of this type of dementia and the presence of auditory dysfunctions is highlighted, as hearing loss has been identified as a modifiable factor associated with Alzheimer's Disease development. This association could lead to the discovery of new therapeutic and preventive mechanisms. The focus of the explored studies is to analyze this possible correlation.

Despite the existence of both older and recent studies indicating a relationship between hearing loss and dementia development, this association requires further analysis to assess its probability, as there are discrepancies among the explored works. Methodological differences existed in the analyzed studies, explaining the variation in obtained results. For example, the assessment of auditory conditions varied across different experiments, affecting the conclusions drawn.

It is worth noting that in studies where the relationship between hyperacusis and the onset of Alzheimer's and other types of dementia was strengthened, the analysis focused on older individuals who had a higher risk of cognitive decline due to age. This emphasizes the limitation of this hypothesis to older patients, who are the focus of the discussion.

The affected pathways due to hearing loss and their relevance in the onset of the pathology were also discussed. In some older studies, both peripheral and central auditory dysfunction directly influenced the probability of developing cognitive decline-related pathologies. However, more recent research suggests that central pathway degeneration is more determinant in this process, while others argue that peripheral pathways play a more significant role.

Interventive auditory treatment, a highlighted aspect, was considered a possible preventive factor in cognitive decline pathology development, given the strong relationship between these two conditions. For example, a study examining the benefits and effects of hearing aids over 18 months in patients with hearing loss observed cognitive improvement, even with a small sample size.

Although the pathophysiology of this association is unknown and underexplored, some hypothesized mechanisms were highlighted. These include a common cause to both conditions (aging, risk age, and inflammatory pathologies), a sensory deprivation mechanism (functional changes leading to reduced white matter in essential cognitive brain regions), a cognitive resource occupation mechanism

(increased cognitive processing to compensate for sensory loss), and a functional and structural interaction mechanism (hearing loss affecting the cortical function of the medial temporal lobe, susceptible to Alzheimer's, or structural changes making the brain more vulnerable to neurological pathologies).

In addition to intrinsic factors, extrinsic factors that act as risk factors for dementia development, such as depression, social isolation, and situations affecting quality of life, may also be caused by hearing loss, especially considering that auditory deficits hinder communication and, consequently, social engagement.

Although there is no definitive proof of this hypothesis, various factors strengthen the correlation based on the analyzed studies. However, some studies contest this hypothesis, as cohort study results were insufficient to prove this relationship. Given the limited and underdeveloped research on this topic, the presence of this association cannot be conclusively affirmed, but if confirmed, it could contribute to significant advances in the prognosis of the described pathology.

DISCUSSION

1- Evidence of Association between Hearing Loss and Alzheimer's Disease

Based on the analysis of the results of this study, it can be stated that there is agreement with the most recent evidence found in the literature. Similar to the analyzed articles, this review presents mixed results, indicating discrepancies in findings related to hearing loss as an explanation for the 'genesis' of Alzheimer's disease. This study emphasizes that limitations and methodological biases in the published studies, along with the lack of adequately assessing auditory processing and cognitive decline through randomized clinical trials, contribute to the causal relationship between hearing loss and dementia remaining somewhat undefined, challenging to evaluate, and requiring further investigation.[5, 6, 17]

The included studies point to a positive association between hearing loss and Alzheimer's. Hearing loss has been designated as an early marker of Alzheimer's disease, potentially acting as a modifiable factor, especially during the prodromal stage of the disease, with the first signs of dementia. A growing body of evidence supports the identification and treatment of modifiable risk factors as a promising strategy to delay the onset or progression of Alzheimer's symptoms. In this perspective, it is estimated that intervention in the early stages of the disease would be equivalent to delaying the onset of dementia by about 5 years. This intervention could, therefore, lead to an approximate 50% reduction in the total prevalence of dementia after a period of 10 years.[3]

It is estimated that hearing loss is responsible for 8% of dementia cases, meaning about 4 million out of 50 million dementia cases worldwide can be attributed to untreated hearing

loss.17 Evidence indicates that even mild hearing loss elevates the long-term risk of cognitive decline and incident dementia. With this, understanding the relationship between hearing loss and dementia has drawn greater attention from public health, especially considering that in the current "Era of Longevity," hearing loss has become an attractive target for dementia prevention strategies, primarily due to the fact that the care foundation for dementia patients relies primarily on communication between the patient and their caregivers.[2, 20]

However, despite its high prevalence and importance for public health, the patient's hearing function is not taken into account for the diagnosis of Alzheimer's disease. Authors such as Yang Liu1 define hearing loss as "highly underestimated," as it can be one of the most neglected deficits in people with Alzheimer's dementia.[20]

Among the evidence of association, Lin et al.1 demonstrated that hearing loss is independently associated with accelerated cognitive decline.[1, 9] In conjunction, a systematic review and meta-analysis of prospective studies identified that hearing loss was associated with a 28% increase in the odds of dementia from all causes.19 Contributing to this finding, the study published in The Lancet in 202019 estimated the population-attributable fraction of hearing loss for dementia at 23.0%, surpassing the rate of any other individual modifiable risk factor, including depression (10.1%), social isolation (5.9%), smoking (13.9%), hypertension (5.1%), and diabetes (3.2%).[9]

Similarly, this Lancet study[19] revealed that people with untreated hearing loss had an increased risk of dementia by over 42%.[19] Although most studies to date have focused on assessing the association between hearing loss and cognitive decline in older adults, two recent population-based cohort studies reported that adults with midlife onset of hearing loss were at a higher risk of dementia.[6]

The first of these studies reported an increased diagnosis rate of dementia before the age of 60 with midlife hearing loss (adjusted hazard ratio = 1.90;17 while the second study observed that the strongest association between hearing loss and dementia was for adults with hearing loss diagnosed between 45 and 64 years (hazard ratio = 1.40 for incident dementia.[6] The findings of these recent studies support the Lancet Commission's position[19] that the increased risk of cognitive decline associated with hearing loss does not only apply to older adults (50-70 years) and that the strongest risk factor in midlife for dementia is hearing loss.[15]

However, some authors [5,17] in this study argue that it was not possible to establish any direct causal link between hearing loss and dementia. Therefore, based on these results, the confirmation of the hypothesis that simply treating hearing loss can decrease the risk of Alzheimer's disease is still not plausible. Therefore, the possibilities of early detection

and labeling of positive patients for biomarkers before the onset of symptoms are still under discussion in the literature, and they are often criticized due to the uncertainty of progression to dementia.[5] In this context, the debate persists on whether hearing loss can be classified as part of 'dementia risk factors,' 'early symptoms of dementia,' or both categories.[5]

In this context, the studies analyzed emphasized the importance of the prodromal phase for Alzheimer's disease. In this phase, which can last up to two decades before the clinical diagnosis of the neurodegenerative disease, hearing loss can vary in classification depending on the temporal window in which it occurs, appearing as a marker of proximity to incipient dementia or a feature of established dementia syndrome (as a phenotype).[13] Therefore, the distinction between early dementia symptoms and causal risk factors becomes a challenging and still-open task.

It is worth noting that the stance of some authors is supported by the discrepancy in results found in the literature, pointing out the various inconsistencies and methodological biases present in the studies, with the presence of confounding factors, difficulty, and limitations in the reliability of tests assessing hearing loss and dementia, making the relationship between hearing loss and Alzheimer's a highly complex research issue. As an example, in some studies, participants with Alzheimer's disease may be in different stages of the disease, or the disease stages were not well-defined (i.e., employing different diagnostic criteria). Subjects may have different ages, and confounding factors may not have been adequately considered and included in the study protocol.[1, 6, 20]

A confounding factor that permeates the relationship between hearing loss and Alzheimer's is that neuropathic changes and microvascular pathology associated with aging increase the risk of hearing loss and cognitive decline.[6] In this spectrum, a review highlighted that the decline not only in hearing but in all our senses is associated with an increased degree of cognitive impairment6. It is estimated that hearing loss affects up to 40% of people over 65 years old and 75% over the age of 80.1 Therefore, it is well known that aging can induce hearing loss; however, in some studies, such as the study by Yang Liu, 20201, the average age of participants in the Alzheimer's and control groups was> 75 years. Thus, it can be inferred that apparently, hearing loss could occur in these individuals even in the control group without Alzheimer's disease.[1]

With this, the relationship between hearing loss, aging, and Alzheimer's was examined, disregarding the fact that the presence of confounding variables, such as age or advanced dementia stage, could mask differences between groups. This perspective was reinforced by a study in the UK [5], where the association between Alzheimer's disease and hearing loss did not remain statistically significant after adjusting for other risk factors as possible

confounders (p=0.057). Some evidence suggests that, alternatively, individuals with cognitive deficits may be erroneously attributing cognitive dysfunction to hearing loss. [4]

The heterogeneity in the ages of participants included in the analyzed studies proved to be a potential confounding factor. Firstly, the average age of participants and gender distribution in the MCSA study [4] are similar to the Health ABC study [2], a biracial cohort of well-functioning adults aged 70 to 79. However, the studies by Lin et al and Gallacher et al report participants with a younger average age, with the latter study [2] including only men with an average age of 56. Therefore, the age differences are noteworthy because, although the average follow-up of the study [4] was shorter, it involves monitoring the age group at higher risk for dementia development. This fact justifies the higher incidence rate of dementia in the study [4] and the Health ABC study [2] than in the studies by Lin et al [1] and Gallacher and colleagues. [4]

Therefore, despite the selection bias towards a population with a higher prevalence of hearing loss, the absence of this relationship in studies [4,6] suggests that selection bias does not significantly impact the results, challenging the overall message of this review that there are other factors related to central processing that can potentiate the impact of hearing assessments.

This finding suggests that individuals at higher risk of developing dementia not only had hearing loss but probably also had additional central processing sensory dysfunction. However, the study supports previous works implicating central processing degradation as a contribution to perceived hearing difficulty and dementia. Thus, hearing loss could be a "warning sign" that cognitive mental capacity is about to decline, thus sharing a common underlying mechanism for both conditions. [4]

In the quest to elucidate the relationship between hearing loss and dementia, the prospective cohort [6] investigated cognition over time in Australian elderly with hearing loss who started using hearing aids. In addition to assessing subjective and objective treatment benefits, such as speech perception and listening ease, researchers also examined how the level of education influenced the extent of hearing loss. The results indicated relative stability and clinically significant improvements in cognition after 18 months of hearing aid use. However, like some studies found in the literature, the study has some limitations, such as the lack of data on potential confounding factors such as education level, ethnicity, socioeconomic status, body mass index, or genetic information. [6] Therefore, as faster cognitive decline is observed in those with worse hearing loss, further research is needed to reveal the causal pathways between hearing loss and cognitive decline. [9,10,16,17] Limitations in the current literature include small sample size, retrospective design, and restricted and inadequate hearing aid assessments such as "self-reported hearing loss" and hearing aid

use, without measuring its benefit or frequency of use. [4] It was analyzed that in studies where hearing loss was objectively measured from the beginning, which often did not happen, other hearing changes were not assessed over time. Other known factors affecting cognition, such as education, social participation, mood, exercise, and diet, were also not considered in some studies. [5,6,20] Regarding cognition, other limitations include the limited assessment of cognitive abilities, for example, only one cognitive task assessed, and/or assessments administered using verbal instructions, introducing a confounding factor for people with hearing loss, who are at a disadvantage even with mild to moderate hearing loss. [6]

Moreover, it should be emphasized that the associations between hearing loss and brain structure depend on the measurement of hearing loss. This study revealed no difference in tonal hearing loss between groups, either because it examined only healthy elderly or initially healthy groups at risk of developing dementia. [3] It should also be considered that the limited reliability of the assessments applied to individuals with dementia, especially in advanced stages, as they have fewer neural resources available and often do not understand speech and consequently perform poorly on tests.

In this population-based prospective study [4], subjective hearing difficulties based on informants were associated with dementia development (HR 1.95, 95% CI 1.45–2.62), while objective measures in formal behavioral audiometry were predictive of worse cognitive test performance over time but not of the clinical diagnosis of dementia. Among 207 incident dementia cases, hearing loss assessed by PTA was not predictive of dementia development (HR increase per 10 dB HL of 0.99, 95% CI 0.89–1.12). Evaluating speech discrimination exclusively, word recognition scores were also not predictive of dementia (HR per 10% reduction of 0.98, 95% CI 0.89–1.07). [4] These findings suggest that the connection between objective measures of hearing loss and dementia may not be as strong as considered previously by other studies. These data support the proposal of previous works that central processing degradation contributes to both perceived hearing difficulty and dementia. Thus, it is observed that central processing deficits could potentiate the effects of hearing loss; however, the association of peripheral hearing loss, detected in formal behavioral audiometric tests, with dementia development may not be as solid and secure evidence as initially seemed. [4]

In general, in a meta-analysis of 36 observational studies, Loughrey et al. (2018) found significant associations between age-related hearing loss and dementia, with a decrease in performance in all domains of cognitive function. [11] Although the overall conclusion of the meta-analysis of research on the effects of hearing aid use on cognition was that hearing loss treatment seemed to improve cognition, the authors observed that methodological limitations

in published research to date do not allow consistent and substantial conclusions about whether the relationship between hearing loss and cognitive decline is causal. [4,6]

In summary, for many studies, information on changes in cognitive function and the rate of these changes over time was not available. The same limitation applies to changes in hearing loss, with a particular lack of information on the benefits of hearing aids and the frequency of device use. Without this information, it is not possible to know if treatment is genuinely effective and, therefore, what the effect of hearing loss, if any, would be on cognition. [6] Overall, although prospective studies have shown positive results favoring the use of hearing aids or cochlear implants to preserve cognitive function, pointing to a lower rate of progression to dementia or an improvement in cognitive abilities, randomized clinical trials are still needed to consolidate causality. [9] Therefore, the wide variability and subjectivity in how cognition and dementia are assessed, the correlational nature of existing research, and the limited way hearing is usually assessed in epidemiological studies (e.g., tonal audiometry vs. more extensive measures, such as word recognition, temporal processing, and frequency selectivity) make the task of making causal inferences very challenging. [9] This is seen as when evaluating cognitive function in subjects with hearing loss, one must take into account that the subject may perform poorly due to not receiving instructions clearly. Thus, hearing loss can distort the results of cognitive tests, especially those predominantly verbal

2. Common Potential Mechanisms - Shared Risk Factors Explaining the Relationship between Hearing Loss and Alzheimer's

There are several potential mechanisms to explain the hearing-cognition relationship. These are not mutually exclusive, and in this review, the supporting evidence for each has been considered. A significant unresolved scientific issue is whether the link between Alzheimer's Disease and hearing loss is related to causal mechanisms (i.e., mediators through which hearing loss causes dementia) or common mechanisms (i.e., a confounding factor that affects both hearing loss and dementia) [9].

2.1) Aging and Neuronal Degeneration

Aging has been associated with an increase in neuronal degeneration, attributed to elevated trophic support imbalance, chronic inflammation, and endothelial dysfunction. Collectively, these factors lead to a common pathology affecting both the cochlea and the ascending auditory pathway (resulting in hearing loss) and the cerebral cortex (resulting in dementia), such as the death of primary auditory neurons (SGNs) and the deposition of NFTs in auditory pathways.[10]

Primary auditory neurons connect hair cells to the cochlear nucleus in the brainstem.

Therefore, age-related SGN loss is a central component of age-related hearing loss and may occur secondarily to the loss of hair cells, which are sustained through trophic support.[10] Recent evidence indicates that the survival of SGNs during physiological aging is multifactorial, dependent on genetic and epigenetic influences. At the cellular and molecular levels, the signaling pathways of free radicals and calcium deserve attention, as they may promote age-related SGN loss. Studies in mice have highlighted that SGN survival depends on various genes encoding neurotrophic factors or neurotrophins, which seem to play a central role in the survival of neurons affected by degenerative processes common to both hearing loss and Alzheimer's Disease.[10]

These neurotrophic factors have significant implications for the framework of neuronal degeneration processes. They are proteins responsible for the development, homeostasis, and survival of the central and peripheral nervous systems. Thus, an imbalance in the interaction of these proteins with their receptors has led to the proposal of a common pathology for both Alzheimer's Disease and Hearing Loss. Since the receptors for neurotrophins NGF, GDNF, and BDNF are found in both the inner ear and the central nervous system and are affected by aging, this shared risk factor is a potential confounding factor in this relationship.[10]

2.2) Deposition of NFTs in Auditory Pathways

The data suggest that neurodegeneration in the auditory system may be an ongoing process in the course of Alzheimer's Disease. Neuropathological studies have reported the formation and deposition of NFTs (hyperphosphorylated TAU protein) in the central auditory pathway long before the detection of Aβ deposition in the brain, one of the main pathogenic pathways associated with Alzheimer's. In contrast, it is noteworthy that Aβ deposition is uncommon in the central auditory pathway.[10]

2.3) Inflammation - Oxidative Stress

It has been proposed that lifestyle-related inflammatory factors (e.g., obesity, sleep quality, and physical activity) could serve as common mediators to chronic stress and the development of Alzheimer's dementia and hearing loss. There is evidence suggesting an inflammatory response in the inner ear of elderly mice, leading to the death of primary auditory neurons and dysfunction in labyrinthine hair cells, induced by oxidative stress and influenced by environmental factors.[10]

Mitochondrial dysfunction is a mediator of oxidative stress, and there are theories suggesting that both hearing loss and Alzheimer's dementia may result from alterations in the following molecular signaling pathways:

2.3.1)Via ROS/VEGF:

With aging, there is an observed increase in reactive oxygen species (ROS) activity and a decrease in their clearance. It is suggested that the accumulation of ROS in cells results in mutations in mitochondrial DNA (mtDNA) and subsequent mitochondrial dysfunction, leading to a reduction in vascular endothelial growth factor (VEGF) levels.[17]

This factor has been proposed as a potential molecular link between hearing loss and Alzheimer's Disease. In Alzheimer's patients, VEGF expression is lower in regions such as the hippocampus, upper temporal lobe, and brainstem. Due to VEGF's involvement in vascular remodeling, endothelial maintenance, and angiogenesis, the reduction of its levels in dementia may indicate altered capillary function, which could modify the efflux of Aβ proteins involved in Alzheimer's pathogenesis. It has also been demonstrated that VEGF binds to amyloid plaques with high affinity, promoting vascular dysfunction, hypoperfusion, and neurodegeneration in Alzheimer's Disease.[17]

2.3.2) Via SIRT1/PGC-1α:

Studies point to the primary regulator of mitochondrial biogenesis, the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), as a potential and promising protagonist in preventing neurodegeneration. With aging, the reduction in SIRT1-PGC-1α expression causes apoptosis of hair cells and neural degeneration due to compromised mitochondrial respiratory function, leading to hearing loss. An animal study demonstrated reduced expression of SIRT1-PGC-1α in the cochlea of elderly mice. Moreover, an in vitro experiment showed that increased SIRT1 expression inhibited cell apoptosis, promoting cell proliferation.[17]

Wang et al.[18] demonstrated, using in vivo and in vitro experiments, that reduced expression of PGC-1α led to altered expression of the enzyme β-secretase 1 (BACE1). Altered BACE1 expression contributes to Aβ production in the brain and the incidence of Alzheimer's Disease. Although further research is needed, the SIRT1-PGC-1α pathway has been suggested as a potential treatment target to prevent individuals with hearing loss from developing Alzheimer's disease in the future.[17]

2.4) Vascular Mechanism

Microvascular complications are common features in both age-related hearing loss and dementia. In light of this, the Lancet Commission identified diabetes mellitus, characterized by microvascular complications, as a common risk factor for both hearing loss and dementia.[17] The reviewed study in this investigation provided the latest evidence that the common trigger for dementia and hearing loss may lie in alterations in the blood-brain barrier (BBB), promoting the development of Alzheimer's disease, and changes in the blood-labyrinth barrier (BLB),

causing hearing loss. The blood-labyrinth barrier is located in the lateral wall of the cochlea and is responsible for the irrigation of the inner ear. Therefore, it is crucial for the proper functioning of auditory and vestibular functions, maintaining homeostasis and transporting nutrients to the inner ear. The hypothesis that hearing loss is a cause of Alzheimer's disease is grounded in the dysfunction of these structures: BLB and BBB. Authors such as Tarawneh HY17, 2022, and Forster[10] emphasized the strength of the common vascular mechanism to explain this relationship, given that many cerebrovascular diseases are associated with the fragility of these structures (e.g., stroke and congestive heart failure), and that microvascular complications associated with diabetes appear to include cognitive impairment and auditory disorders as common comorbidities.[10]

3) Adjacent Mechanisms - Independent in the Hearing Loss and Alzheimer's Relationship

3.1) Changes in Brain Structure:

Overall, the collected data provide evidence that, in addition to the cognitive-auditory connection, an association has been reported between hearing loss and brain atrophy in both gray and white matter. It has been found that a higher degree of hearing loss is correlated with a smaller volume of gray matter in brain regions associated with auditory perception (e.g., superior temporal lobe) and cognition (e.g., hippocampus, para-hippocampus). Therefore, the right hippocampal atrophy in individuals with moderate to severe hearing loss "appears" approximately 8 years older, considering that normal shrinkage is approximately 0.5% annually for individuals over 60 years old.[3]

Regarding the interconnection between dementia and hearing loss, it is possible that Alzheimer's-related neuropathology is responsible for the accelerated decline of brain structures by exacerbating or worsening the decline in speech processing in adverse auditory conditions. Lin et al.[1] showed that, in cognitively normal older adults, those with greater hearing loss experienced accelerated volume loss compared to those with normal hearing. This accelerated volume loss was observed in various regions of the temporal lobe (i.e., upper, middle, and lower right temporal gyri and para-hippocampus) that are recruited for auditory processing, semantic memory functioning, and cognitive processing. [3]

The study [3] cautioned that Alzheimer's patients exhibited greater atrophy in the frontal, temporal, and parietal lobes. It is evident that speech recognition in noise may be disproportionately impaired in older individuals with Alzheimer's Disease, and interestingly, in this study, older individuals with greater tonal hearing loss had greater cortical thickness in the left superior temporal gyrus (STG) (or Wernicke's area) and the right pars opercularis (or Broca's area), responsible for spoken language comprehension and language production, respectively.[3]

Another proposed structural mechanism relates to neurofibrillary changes related to Alzheimer's Disease found in the Medial Temporal Lobe. This mechanism suggests that hearing loss modifies cortical activity in the Medial Temporal Lobe (MTL), an important area for memory processing and episodic memory, which may be interrelated with Alzheimer's pathology in the same region. It is suggested that hearing impairment may cause changes in neuronal activity in the structures of the Medial Temporal Lobe, which in turn may cause or increase Alzheimer's neuropathology.[11]

Although the structures of the Medial Temporal Lobe are not classically considered part of the auditory system, animal models support their role in auditory processing. The study [11] theorized about the critical interaction between auditory cognitive processing in the Medial Temporal Lobe (MTL) and dementia pathology.

Two potential hypotheses were formulated about how auditory-linked brain activity may be related to Alzheimer's disease with degeneration in the Medial Temporal Lobe area. The first is related to neuronal distress from having to work intensively in the face of hearing loss. The other idea involves an imbalance in brain rhythmic activity, driven by changes in how sensory information reaches the Medial Temporal Lobe, known as "driving inputs."[11]

3.2) SENSORY DEPRIVATION MECHANISM - DECREASED COGNITIVE RESERVE

In this hypothesis, the possible linking mechanism is that hearing loss leads to a decrease in cognitive processing stimulation. The idea is that auditory deprivation creates an impoverished environment, particularly with decreased speech and language, causing deterioration of brain resources and low availability of cognitive resources. This change in brain structure and function is a risk factor for the subsequent development of dementia.[3] A large number of studies in animals, especially rodents, have demonstrated changes in the brain and behavior resulting from the experience of enriched environments (as opposed to impoverished environments). Continuous impoverishment of auditory input, with reduced sensory inputs, has widespread effects throughout the cortex, leading to gray matter atrophy and a decrease in cognitive reserve.[3,7]

The concept of cognitive reserve posits that individual differences in the ability to optimize cognitive performance through the differential recruitment of brain networks and alternative strategies allow some individuals to better cope with neuropathology compared to others. As seen in the study, low education is associated with a worse prognosis for Alzheimer's disease because individuals with constant stimulation for plasticity and higher cognitive reserves have shown to be more resistant to brain pathology

and better able to mitigate the clinical progression of the disease.[6] However, the effects of hearing loss on cognitive reserve are still a matter of discussion.[9]

3.2.2)COGNITIVE OVERLOAD

A third mechanism, also referred to as "cognitively demanding listening" or "cognitive overload," is based on the idea that individuals with hearing impairment need to mobilize greater cognitive resources to hear, making these resources unavailable for other aspects of higher cognition (such as attention, working memory, or language processing) when they are "busy" during listening.[11]

Research shows that under conditions where auditory perception is challenging, such as hearing loss, individuals experience a higher cognitive load and may more easily deplete their cognitive reserve. Studies have demonstrated that individuals with hearing loss allocate more neural resources to facilitate auditory processing, thus diverting resources from other functions of higher cognitive processing, resulting in poorer performance in cognitive assessments (e.g., memory tests). Furthermore, it has been shown that this reallocation of neural resources and depletion of cognitive reserves may lead to an earlier clinical presentation of dementia.[9]

The study supporting the connection between the development of hearing loss and Alzheimer's raised the possibility that those with greater hearing loss in tonal audiometry probably rely more on multisensory cues (e.g., visual speech cues) and working memory during speech comprehension, leading to a greater need for mobilizing cognitive resources and consequently, greater changes in the right pars opercularis. Similarly, the right pars opercularis is involved in speech processing, particularly in speech perception tasks involving vowel tone discrimination, syllable discrimination, sentence pitch, and prosody processing.[11]

In the context of "cognitive reserve depletion," there is also an increase in brain activity in the temporal lobe and overload of a wide network of neurons during speech analysis in noise, competing for cognitive resources, which are also necessary for other aspects of higher cognition. The findings of this research suggested that individuals with greater structural integrity in brain regions recruited during cognitive processes and during speech in noise may be able to use these regions to compensate for difficulties in understanding speech in noise with reduced and less efficient activation of the medial temporal lobe.[11]

4) Future Perspectives - Potential Interventions Discussed in the Literature

Approximately two-thirds of adults over 70 years old are affected by hearing loss, yet less than 20% of adults with hearing loss receive treatment (e.g., hearing aids). In the current scenario, where hearing loss is highly prevalent in the elderly and severely undertreated, more and

more research views hearing loss as an attractive target for intervention to prevent or delay dementia in older adults. However, a causal link between these two conditions must be investigated before making any definitive recommendations for prevention and treatment. Randomized clinical trials are needed to determine if hearing rehabilitation can stem the wave of dementia looming in the global elderly population.[9]

In the context of screening, a review assessed the role of central auditory processing function in Alzheimer's disease (AD) and its preclinical stages. Tarawneh and colleagues concluded that a specific battery of tests, such as measuring P300 potentials often associated with cognitive processes like attention and working memory, could be used as a biomarker to identify elderly individuals at early risk of cognitive impairment in clinical settings.[16]

The results obtained in Study 1 also suggest that recording Brainstem Auditory Evoked Potentials (BAEP) could serve as a simple, sensitive, and non-invasive screening tool for the early detection of Alzheimer's disease and lesion localization, particularly in the early (preclinical) stage of Alzheimer's. BAEP is a routine hearing function test in the clinical environment and can assess the function and integrity of the auditory pathway from spiral ganglion neurons to auditory centers.[1] However, despite the growing body of evidence, a 2018 report from the United States Preventive Services Task Force found insufficient evidence to recommend screening or treating hearing loss in adults aged 50 and older.[8]

Regarding future directions on the effectiveness of early interventions in Alzheimer's disease, the first systematic review and meta-analysis of 30 studies (including 40 samples) concluded that while people with hearing loss had worse cognition compared to those with normal hearing, those who used hearing aids had better cognition than those who remained untreated.[6]

From this perspective, a study by Cuoco et al. revealed that 6 months of hearing aid use brought positive results to cognitive function in participants with mild hearing loss but was not beneficial in more severe cases. The authors suggest that auditory rehabilitation in individuals with mild hearing impairment may be more effective in reducing cognitive decline.[17] However, the authors emphasize that a longer follow-up period is necessary, and more research is indispensable to fully understand the effect that hearing aid use can have on those with mild hearing loss to more severe cases, elucidating, especially, the affected mechanisms, which still remain unclear and uncertain.

Additionally, it was found that treating hearing loss with hearing aids or cochlear implants has positive impacts on mental health and results in substantial improvement in the quality of life in adults with mild hearing loss. Collectively, the above research indicates that treating hearing loss may not have the potential to reverse cognitive decline, as it is unlikely to be able to alter the course of neuropathic changes and microvascular pathology related to aging. However, there is evidence that hearing aid use

can significantly improve speech perception and communicative ability, potentially enhancing an individual's quality of life, preserving cognitive function and social integration, and consequently slowing the progression rate to dementia. Given that social isolation is associated with increased systolic blood pressure and corticosteroid levels and is as strong a risk factor for morbidity and mortality as other well-known risk factors such as smoking, obesity, and sedentary lifestyle, it is also possible that the reduction of social isolation due to hearing aid use can improve physical health and thus reduce the risk of dementia.[6, 9]

CONCLUSION

The development of the present study has allowed us to understand that accurate diagnosis, based on clinical manifestations, is a crucial element that ensures a prompt approach to initial treatment. Identifying the relationship between hearing loss and the later development of Alzheimer's becomes fundamental.

Therefore, it is concluded that the refinement of diagnostic techniques, updates in diagnosis, and advances in Alzheimer's studies, especially regarding rarer forms of the disease, along with signs such as hearing loss, contribute to a better quality of life for patients and families facing this condition. In light of this, it is hoped that this study can contribute to the understanding of clinical manifestations related to Alzheimer's and enable the continuous scientific advancement in the medical approach to patients.

REFERÊNCIAS

1. Liu, Y., Fang, S., Liu, L.-M., Zhu, Y., Li, C.-R., Chen, K., & Zhao, H.-B. (2020). Hearing loss is an early biomarker in APP/PS1 Alzheimer's disease mice. Neuroscience Letters, 717, 134705. doi:10.1016/j.neulet.2019.134705

2. Deal JA, Betz J, Yaffe K, Harris T, Purchase-Helzner E, Satterfield S, Pratt S, Govil N, Simonsick EM, Lin FR; Health ABC Study Group. Hearing Impairment and Incident Dementia and Cognitive Decline in Older Adults: The Health ABC Study. J Gerontol A Biol Sci Med Sci. 2017 May 1;72(5):703-709. doi: 10.1093/gerona/glw069.

3. Giroud N, Pichora-Fuller MK, Mick P, Wittich W, Al-Yawer F, Rehan S, Orange JB, Phillips NA. Hearing loss is associated with gray matter differences in older adults at risk for and with Alzheimer's disease. Aging Brain. 2021 Jun 28;1:100018. doi: 10.1016/j.nbas.2021.100018.

4. Marinelli JP, Lohse CM, Fussell WL, Petersen RC, Reed NS, Machulda MM, Vassilaki M, Carlson ML. Association between hearing loss and development of dementia using formal behavioural audiometric testing within the Mayo Clinic Study of Aging (MCSA): a prospective population-based study. Lancet Healthy Longev. 2022 Dec;3(12):e817-e824. doi: 10.1016/S2666-7568(22)00241-0.

5. Nedelec T, Couvy-Duchesne B, Monnet F, Daly T, Ansart M, Gantzer L, Lekens B, Epelbaum S, Dufouil C, Durrleman S. Identifying health conditions associated with Alzheimer's disease up to 15 years before diagnosis: an agnostic study of French and British health records. Lancet Digit Health. 2022 Mar;4(3):e169-e178. doi: 10.1016/S2589-7500(21)00275-2.

6. Sarant J, Harris D, Busby P, Maruff P, Schembri A, Lemke U, Launer S. The Effect of Hearing Aid Use on Cognition in Older Adults: Can We Delay Decline or Even Improve Cognitive Function? J Clin Med. 2020 Jan 17;9(1):254. doi: 10.3390/jcm9010254.

7. Sanchez VA, Arnold ML, Reed NS, Oree PH, Matthews CR, Clock Eddins A, Lin FR, Chisolm TH. The Hearing Intervention for the Aging and Cognitive Health Evaluation in Elders Randomized Control Trial: Manualization and Feasibility Study. Ear Hear. 2020 Sep/Oct;41(5):1333-1348. doi: 10.1097/AUD.0000000000000858.

8. Deal JA, Goman AM, Albert MS, Arnold ML, Burgard S, Chisolm T, Couper D, Glynn NW, Gmelin T, Hayden KM, Mosley T, Pankow JS, Reed N, Sanchez VA, Richey Sharrett A, Thomas SD, Coresh J, Lin FR. Hearing treatment for reducing cognitive decline: Design and methods of the Aging and Cognitive Health Evaluation in Elders randomized controlled trial. Alzheimers Dement (N Y). 2018 Oct 5;4:499-507. doi: 10.1016/j.trci.2018.08.007.

9. Chern A, Golub JS. Age-related Hearing Loss and Dementia. Alzheimer Dis Assoc Disord. 2019 Jul-Sep;33(3):285-290. doi: 10.1097/WAD.0000000000000325.

10. Förster CY, Shityakov S, Scheper V, Lenarz T. Linking Cerebrovascular Dysfunction to Age-Related Hearing Loss and Alzheimer's Disease-Are Systemic Approaches for Diagnosis and Therapy Required? Biomolecules. 2022 Nov 19;12(11):1717. doi: 10.3390/biom12111717.

11. Griffiths et al., How Can Hearing Loss Cause Dementia?, Neuron (2020), https://doi.org/10.1016/j.neuron.2020.08.003

12. Jafari Z, Kolb BE, Mohajerani MH. Age-related hearing loss and tinnitus, dementia risk, and auditory amplification outcomes. Ageing Res Rev. 2019 Dec;56:100963. doi: 10.1016/j.arr.2019.100963.

13. Johnson JCS, Marshall CR, Weil RS, Bamiou DE, Hardy CJD, Warren JD. Hearing and dementia: from ears to brain. Brain. 2021 Mar 3;144(2):391-401. doi: 10.1093/brain/awaa429.

14. Nadhimi Y, Llano DA. Does hearing loss lead to dementia? A review of the literature. Hear Res. 2021 Mar 15;402:108038. doi: 10.1016/j.heares.2020.108038.

15. Pérez-González D, Schreiner TG, Llano DA, Malmierca MS. Alzheimer's Disease, Hearing Loss, and Deviance Detection. Front Neurosci. 2022 Jun 2;16:879480. doi: 10.3389/fnins.2022.879480.

16. Ralli M, Gilardi A, Stadio AD, Severini C, Salzano FA, Greco A, Vincentiis M. Hearing loss and Alzheimer's disease: A Review. Int Tinnitus J. 2019 Sep 4;23(2):79-85. doi: 10.5935/0946-5448.20190014.

17. Tarawneh HY, Jayakody DMP, Sohrabi HR, Martins RN, Mulders WHAM. Understanding the Relationship Between Age-Related Hearing Loss and Alzheimer's Disease: A Narrative Review. J Alzheimers Dis Rep. 2022 Sep 12;6(1):539-556. doi: 10.3233/ADR-220035.

18. Wang HF, Zhang W, Rolls ET; Alzheimer's Disease Neuroimaging Initiative; Li Y, Wang L, Ma YH, Kang J, Feng J, Yu JT, Cheng W. Hearing impairment is associated with cognitive decline, brain atrophy and tau pathology. EBioMedicine. 2022 Dec;86:104336. doi: 10.1016/j.ebiom.2022.104336.

19. Jiang F, Mishra SR, Shrestha N, Ozaki A, Virani SS, Bright T, Kuper H, Zhou C, Zhu D. Association between hearing aid use and all-cause and cause-specific dementia: an analysis of the UK Biobank cohort. Lancet Public Health. 2023 May;8(5):e329-e338. doi: 10.1016/S2468-2667(23)00048-8.

20. Bosmans J, Jorissen C, Cras P, et al. Impact of hearing loss and vestibular decline on cognition in Alzheimer's disease: a prospective longitudinal study protocol (Gehoor, Evenwicht en Cognitie, GECkO). BMJ Open 2020;10:e039601. doi:10.1136/ bmjopen-2020-039601

Observação: os/(as) autores/(as) declaram não existir conflitos de interesses de qualquer natureza.