Hearing loss and Alzheimer’s disease: A Review

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ABSTRACT

Many studies have focused on the relationship between hearing loss and Alzheimer’s Disease (AD). The mechanisms and causal relationship of this association are still partially unknown, and several theories have been proposed. The most accredited hypothesis is that peripheral hearing deprivation may lead to social isolation and subsequently to dementia. Another hypothesis supports the role of hearing loss on cortical processing, with an increased assignment of cognitive resources to auditory processing rather than to other cognitive processes; other theories suggest changes in the brain structure following reduced peripheral auditory stimulation, or a common cause to both conditions. These preliminary findings clearly delineate the importance of further research aimed at investigating hearing impairment in AD, to a) allow early detection of people with predisposition to AD, b) improve the quality of life in AD patients with hearing loss and c) possibly prevent the progression of the disease treating the hearing impairment. In this review paper, the authors discuss current evidence on the association between hearing impairment and dementia, the identification of peripheral and central auditory dysfunction in at-risk patients as a potential early indicator of incipient AD, and the clinical aspects and the management of patients with AD and hearing loss.

Keywords: Alzheimer’s disease; hearing loss; Presbycusis; dementia.
INTRODUCTION

Alzheimer’s Disease (AD) is an acquired condition characterized by progressive cognitive and behavioural decline and is the second most common form of dementia in the general population after mild cognitive impairment. It is estimated that approximately 20 million people worldwide are affected from AD; however, only a portion of them is correctly diagnosed. In the United States, around 5.5 million people have AD; of these, most (nearly 5.3 million) are 65 year old and older while only 200,000 have a young-onset form of AD. The National Institute on Aging indicated that the prevalence of AD doubles every five years beyond the age of 65; therefore, as the population ages, AD impacts a greater percentage of people. It has been hypothesized that the total number of individuals with AD in the United States could increase to as high as 16 million by 2050. The correct identification of AD risk factors can be helpful in intercepting the disease and slowing its progression. At the moment, it is well known that age, family history, and biological inheritance are risk factors for AD; however these factors cannot be modified and, thus, cannot contribute to reduce disease progression. The identification of other possibly modifiable risk factors may therefore help in the management of patients with AD.

Aging is the most prevalent cause of sensorineural hearing loss. The presence of hearing loss in the elderly is described by the term “presbycusis”; it typically presents as sensorineural hearing loss characterized by loss in the high frequencies (Figure 1) and sometimes may be associated to the presence of cochlear dead regions. Presbycusis, the second most common health issue of the aged population after arthritis, may present as a multifactorial hearing disorder characterized not only by general hearing disability, but also impaired recognition of words, especially in noisy environments, tinnitus and hyperacusis. Recent studies have also suggested a role of synaptopathy between inner hair cells and sensory neurons in presbycusis.

The ability to communicate with friends and family mainly depends on one’s ability to hear and process speech and environmental sounds. When individuals develop presbycusis, they are hampered in their ability to converse by phone or face to face; these problems often have a significant impact on social life and may favor the onset of depression, cognitive decline and dementia. Epidemiological studies have described an association between hearing loss and cognitive impairment including AD; other studies have shown that hearing disorders may be a potentially modifiable risk factor of AD. In a review published in 2018, Swords et al. reported that both peripheral and central auditory system alterations can be found in early AD stages and they could be early indicators of the disease, thus suggesting to investigate peripheral and central auditory dysfunction in at-risk subjects as this could be an effective strategy to diagnose AD in its early stages and initiate therapeutic interventions aimed at enhancing the quality of life of AD patients and hopefully have a role in disease progression.

These preliminary findings clearly delineate the importance of further research aimed at investigating hearing impairment in AD, to a) allow early detection of people with predisposition to AD, b) improve the quality of life in AD patients with hearing loss and c) possibly prevent the progression of the disease treating the hearing impairment.

ASSOCIATION BETWEEN HEARING LOSS AND ALZHEIMER’S DISEASE

Hearing loss and AD are common conditions in older adults with a significant impact on quality of life. Epidemiological studies have demonstrated a correlation between these conditions and the role of hearing loss as a modifiable risk factor for the development of AD. An

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**Figure 1:** Typical audiogram in presbycusis. Pure tone audiometry presents a sensorineural hearing loss characterized by loss in the high frequencies.
observation study conducted by Uhlmann et al. in 1986 on 156 patients with AD suggested hearing loss being an indicator for the development of cognitive dysfunction. A few years later, the same authors confirmed these preliminary findings reporting that hearing loss was significantly and independently correlated with the severity of cognitive dysfunction in an AD case-control study matched for age, sex, and education status. Since then, several studies confirmed the association between AD and hearing impairment; however, the physiopathological mechanisms and causal relationship of this association remain unknown.

There are several theories that support the correlation between hearing loss and AD. The most accredited hypothesis is that hearing impairment may lead to sensory deprivation and social isolation that subsequently leads to dementia. Another theory suggests that hearing loss may affect cortical processing through the increase of the cognitive load and the assignment of cognitive resources to auditory processing rather than to other cognitive processes. This hypothesis is also based on the evidence that auditory processing needs more cognitive resources when the auditory signal is deteriorated, thus resulting in the degradation of other cognitive processes. Another theory proposes that decreased auditory stimulation causes changes in brain structure making the brain more vulnerable to factors able to cause brain pathologies, such as neurofibrillary tangles, Aβ accumulation, and micro-vascular disease, thus leading to a higher risk of dementia. Other studies have speculated that there may be a common cause to both diseases and therefore hearing loss may be an early symptom of dementia; in fact, the auditory and the memory areas are strictly related and an atrophy in one of the two may impact on the other (Figure 2).

Chang et al. attempted to discover the mechanisms underlying this association using animal models to elucidate the time course of cognitive decline following hearing loss and then evaluating changes in cognitive function and synaptic protein levels after induction of the hearing loss. They found that degeneration in the central auditory pathways may cause the degeneration of the synapses of hippocampus or increase the vulnerability of these synapses to damage. This hypothesis is supported by findings showing that focal cortical infarction of brain regions that are remote but connected to the hippocampus can induce neuronal loss in the hippocampus.

Shen et al. have examined the involvement of a molecular pathway underlying the association between hearing loss and AD. The authors summarized the enzymes and proteins that may have a role in the pathogenesis of both age-related hearing loss and AD and suggested that an abnormal expression of these structures, including Vascular Endothelial Growth Factor (VEGF), SIRT1-PGC1α, and LKB1 (or CaMKKβ)-AMPK, may cause both AD and dysfunction of cochlear hair cells. In addition, they hypothesized that these two conditions may also influence the progression of each other as they have common pathological pathways and targets.

Although a large number of studies have investigated this relationship, there is still controversy about the role of peripheral hearing impairment and central auditory processing in AD. Peripheral hearing loss might have a more direct role on neurodegenerative processes at the base of dementia. In fact, hearing loss in older adults positively correlates with reduction of tissue volume in auditory cortex, temporal lobe, and the whole brain, and may lead to functional reorganization of auditory cortical networks. The role of the central auditory processing in AD is still not well understood. Alterations in central auditory processing may reflect abnormal cortical mechanisms employed in the analysis of auditory scenes this is supported by the evidence that even minor alterations in auditory cortical evoked potentials can precede clinical symptoms of the neurological condition in young patients with pathogenic AD mutations.

A recent systematic review from Thomson et al. included 17 articles that indicate an association between hearing...
loss and dementia or cognitive decline, although a large variation in the methods used for ascertaining hearing loss and dementia was present in the included articles. Hearing loss was mainly evaluated through the peripheral auditory function with Pure Tone Audiometry (PTA), while only a fraction of the included studies measured central auditory function. Dementia was mainly defined using the Mini Mental State Exam (MMSE). The authors concluded that although they found a significant variability in the methods used to evaluate patients in the included studies, and they mainly evaluated peripheral hearing loss, each of them demonstrated that hearing loss was associated with higher incidence of dementia in older adults.

Results of other studies instead reported almost-normal pure tone thresholds in patients with AD, thus suggesting that AD pathology may be mainly associated with central, rather than peripheral, auditory dysfunction. Central auditory dysfunction should be suspected in subjects that report difficulties in understanding speech in background noise16. Gates et al.52 reported central auditory dysfunction as a prelude of AD performing central auditory processing tests in 274 elderly subjects with a mean age of 79.6 years and monitored them for a period of four years. The authors found that the results of central auditory processing tests were significantly worse in the patients that developed dementia during follow up and recommended to evaluate central auditory function in seniors complaining of hearing difficulty and in those specifically reporting difficulties in hearing in noise. Another study on patients in the Framingham dementia cohort65 found that severe central auditory dysfunction, based on low scores on the Synthetic Sentence Identification with Ipsilateral Competing Message test, could be an indicator of dementia diagnosis within 3 to 12 years. In support of these hypotheses, a magnetic resonance brain image study by Lin et al.60 indicated that hearing loss is correlated with atrophy of the whole brain; such changes were more evident in the right temporal lobe.

**CLINICAL FEATURES OF HEARING LOSS IN ALZHEIMER’S DISEASE**

Hearing impairment in AD does not have specific characteristics that differentiate it from age-related hearing loss or from other forms of sensorineural hearing impairment; however, certain evidence suggests auditory cognitive disorders in AD19. It has been reported that patients with AD may experience more listening difficulties than expected from the degree of hearing loss diagnosed with PTA and may have a reduced benefit from the use of hearing aids58-59. Commonly, AD patients report difficulties in listening and in understanding the meaning of words in the presence of background noise; this contributes to the avoidance of social environments. However, this condition may also be present in otherwise healthy older adults with presbycusis60. Furthermore, patients with AD may have various abnormal behavioral responses to sounds, with an alteration in the mechanisms of matching sounds with past experiences61 leading to a poor or an aberrant perception of sounds. The first case constitutes an auditory agnosia, which consists in the impairment in sound perception and identification despite intact hearing, and may be limited to specific sounds, while the second may manifest as auditory hallucinations most probably deriving from aberrant cortical activity62. Last, hyperacusis - the intolerance to certain everyday sounds that cause significant distress and impairment in daily activities63,64 has been also reported in patients with AD65.

**CLINICAL MANAGEMENT OF PATIENTS WITH ALZHEIMER’S DISEASE AND HEARING LOSS**

A symptom-based clinical approach to patients presenting with cognitive impairment and hearing loss has been proposed by Hardy et al.19. The authors suggested that the assessment of hearing loss in patients with a neurological diagnosis of dementia, including AD, should initiate with clinical history evaluation to highlight key auditory symptoms, followed by a complete audiological and neurological examination. Audiological evaluation should include PTA, oto-acoustic emissions and brainstem auditory evoked potentials. Additional auditory tests, such as measurement of speech in noise perception, gap-in-noise perception, dichotic listening and tone-in noise audiometry66,67 can be used as they more closely reflects realistic hearing impairment and may indicate alterations in cortical auditory processing. At this regard, Rahman et al.68 evaluated central auditory processing in 150 patients with a neurological diagnosis of mild cognitive impairment and compared the results to 150 age, sex and PTA-matched controls; the authors used selective auditory attention test, auditory fusion test, pitch pattern sequences test, and dichotic digits test and found a significant alteration of central auditory processing test scores in patients in the study group compared to those in the control group.

General neuropsychological assessment should then be performed to identify executive or attention deficits that can also be present in these patients and may confound the results of auditory tests. Diagnosis should always include brain magnetic resonance imaging to exclude concurrent retrocochlear conditions i.e. vestibular schwannoma69,70 and further characterize the neuroanatomical basis of the auditory deficit19.

The management of patients with AD and hearing loss requires a multidisciplinary approach by audiologists, speech and language therapists, and neurologists and should include the immediate correction of any treatable cause of hearing impairment, such as the removal of earwax71,72, the use of hearing aids and other listening devices and specific strategies such as the employment of written communication and electronic devices,
the reduction of background noise, the avoidance of subjective distressing sounds and the use of competing techniques for auditory hallucinations.

CONCLUSION

Much evidence has accumulated in the past decades on the association between hearing loss and AD; however the underlying mechanisms of this association remain partly unclear. Large-scale studies that employ on one side comprehensive peripheral and central hearing function evaluation and on the other a rigorous evaluation of AD diagnosis and brain magnetic resonance imaging are necessary to robustly assess the association of hearing impairment and AD. Furthermore, the understanding of the mechanisms underlying this association is still partial and requires specifically-aimed study protocols.

Recent studies have shown a correlation between hearing loss and changes in brain structures of animal models that, together with changes in the molecular pathway at the base of these pathologies, could carry forward the future of research in this field. In fact, the identification of potentially common targets or pathways could allow the development of drugs aimed at this common target. On a clinical perspective, the correct identification of hearing loss in patients with AD is crucial, as its treatment has been shown to significantly improve the global condition of these patients. The management of patients with AD and hearing loss requires a multidisciplinary approach that should include audiologists, speech and language therapists, and neurologists.

CONFLICT OF INTEREST

The Author declares no potential conflict of interest on publishing this paper.

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