Research Article

Archives of Nursing and Care

Health Care: Alzheimer's Disease Diagnosis and Patient Management

Abstract

Alzheimer's disease (AD) is a chronic neurodegenerative disorder affecting a major class of silver citizens. The disorder shares a mutual relationship on account of its cellular and molecular pathophysiology with type-II diabetes mellitus (DM). Chronic DM increases the risk for AD. Emerging evidence recommended that resistance in insulin production develops cognitive dysfunction, which generally leads to AD. Repurposing of antidiabetic drugs can be effective in preventing and treatment of the neurodegenerative disorder. Limitations of antidiabetic drugs restrict the repurposing of the drugs for other disorders. The following paper provides an up-to-date review of clinical issues and relevant research. Research related to the methods of the earliest possible detection of AD is ongoing. Health care professionals should play a critical role in differentially diagnosing AD patients, as well as supporting their families. Therefore, nanotechnological intervention plays a significant role in the treatment of neurological disorders. In this review, we discuss the common cellular and molecular pathophysiologies between AD and type-II DM, the relevance of in vivo models of type II DM in the study of AD, and the repurposing of antidiabetic drugs and the nanodelivery systems of antidiabetic drugs against AD.

Keywords: Alzheimer's disease • Antidiabetic drugs • Nano delivery systems • Health care

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Received: 02-Aug-2023, Manuscript No. OANC-23-96755; **Editor assigned:** 04-Aug-2023, PreQC No. OANC-23-96755 (PQ); **Reviewed:** 18-Aug-2023, QC No. OANC-23-96755; **Revised:** 24-Aug-2023, Manuscript No. OANC-23-96755 (R); **Published:** 30-Aug-2023; **DOI:** 10.37532/oanc.2023.6(4).74-78

Introduction

AD most frequently presents with episodic memory impairment as the earliest and most prominent feature, with additional deficits in language, semantic memory, executive functioning, visuospatial abilities, and functional impairment that emerge over the disease course. A common misconception is that AD is a "normal" or expected occurrence of aging, and it is part of the typical trajectory of age-related cognitive decline. Rather, healthy aging has been found to be associated with relatively stable performance on measures of cognitive functioning when measured longitudinally. However, cross-sectional studies have indicated that some domains of cognitive functioning do in fact decline with age [1]. As individuals live to advanced ages, it can become more challenging to differentiate between the subtle cognitive declines that accompany aging and those that signify early dementia.

The trajectory of AD is characterized along a continuum, ranging from healthy aging to preclinical AD, mild cognitive impairment (MCI), and dementia. Pathological changes that underlie AD begin to accumulate for years, or even decades, before emotional, physical, or cognitive symptoms emerge, eventually reaching a threshold at which the onset of a gradual and progressive decline in cognition occurs. Preclinical AD constitutes the presymptomatic phase during which characteristic neuropathological changes begin to emerge [2].

The transitional period between normal cognitive functioning and dementia is referred to as Mild Cognitive Impairment; the most common form, the one most likely to progress to AD, is amnestic MCI. AD is often referred to as a family disease because of the tremendous impact that befalls the patient's immediate social support system. By identifying AD in its early stages, recommendations for the most current or efficacious interventions can be made, with the goal of slowing disease progression. Early detection may provide patients and their families with an opportunity to begin the discussion of future caregiving, finances, and end-of-life issues before the patient's autonomous decision-making skills deteriorate. Also, implementing caregiver interventions, such as referral to support groups, psychoeducation, and counseling or psychotherapy, can also assist patients and their families.

AD is characterized by progressive degenerative neuronal changes, with associated global deterioration of cognitive and personality functioning. This pathological sequence preferentially begins in the medial temporal lobe structures responsible for memory and then progresses to the frontal, temporal, and parietal areas, with relative sparing of the motor and sensory cortical regions and subcortical regions. The most widely held theory accounting for the pathological changes underlying disease process is the amyloid cascade hypothesis, positing that the primary, triggering event is the excessive accumulation and clumping together of beta-amyloid, leading to the formation and deposition of amyloid plaques throughout the medial temporal lobe and cerebral cortex [3]. A resultant cascade of events occurs, including neuronal damage, disrupted neuronal communication, inflammation, and the initiation of a second abnormal protein process the accumulation of neurofibrillary tangles.

NFTs are composed of an abnormal form of the intraneuronal protein tau, which normally plays a role in structural support and cellular communication. Abnormal processes cause the tau protein to misfold and aggregate into NFTs, ultimately leading to a breakdown in neuronal function and communication and eventually cell death. The accumulation of NFTs occurs in a hierarchical pattern, beginning primarily in the medial temporal lobe, gradually progressing into the limbic system, and eventually spreading throughout the neocortex. There is evidence that the presence of both amyloid plaques and NFTs is required for AD to develop.

Researchers continue to search for tools that can offer the same degree of diagnostic certainty during life that postmortem brain tissue examinations offer. There are currently five biomarkers which show the most promise as indicators of AD pathology organized into two categories: biomarkers of beta-amyloid accumulation and biomarkers of neuronal degeneration or injury [4]. The accumulation of beta-amyloid can be detected through the use of radioactive tracers in conjunction with positron emission tomography (PET) imaging, as well as through the analysis of beta-amyloid levels in the cerebrospinal fluid. Analysis of CSF levels of tau has also been found to indicate neuronal degeneration associated with NFT accumulation. Fluorodeoxyglucose-(FDG-) PET imaging can be employed to detect hypometabolism in the temporoparietal region, which has been shown to effectively differentiate AD from normal controls. Finally, structural magnetic resonance imaging (MRI) can be used to detect the characteristic pattern of pronounced atrophy in the medial temporal lobes that often occurs in mild to moderate AD.

While biomarker research holds promise for early detection and diagnosis of AD, standardized guidelines are still being developed for determining cut-points for diagnosis. Thus, the use of biomarker data is currently indicated primarily for research purposes. Newly approved amyloid imaging techniques are beginning to be used in order to supplement the results of other diagnostic evaluations.

The Diagnostic and Statistical Manual of Mental Disorders is a tool which is widely employed in clinical settings for diagnosing AD. The recently released version, the DSM-5, contains updated criteria for diagnosing AD which parallel the NIA-AA diagnostic guidelines [5]. It is imperative for clinicians to familiarize themselves with these revised criteria, listed within the Neurocognitive Disorders section, as the criteria contained in the prior DSM-IV-TR are not reflective of the current state of the AD literature.

The initial presentation of AD typically involves anterograde amnesia resulting from progressive declines in episodic memory. Specific memory tests may reveal deficits in the encoding and consolidating of new information into long term memory as evidenced by rapid forgetting after a time delay and lack of improvement even when recognition cues are provided. On episodic memory tasks, AD patients commonly commit more errors of intrusion and perseveration, have difficulty employing semantic encoding tactics, and demonstrate less of a primacy effect when compared to normal elderly individuals. As memory impairment begets functional decline, some of the first overt signs of AD often noted by family members include repeating oneself in conversations, misplacing items, becoming lost while driving, burning meals while cooking, and difficulty managing finances. With regard to remote memory, a pattern emerges in the early stages of the disease in which older memories are relatively

spared, while those from the more recent past are lost.

Deficits in semantic memory and language may become evident early in the course of AD, as well. These difficulties are thought to result from the degenerative disease process causing a breakdown in the brain's interconnected network of general knowledge for concepts, facts, words, and their meaning. Impairment may be detected on tests of verbal fluency, with the tendency to perform relatively worse on tasks requiring generation of words from a given category versus generation of words that begin with a particular letter of the alphabet. Patients are unable to employ clustering strategies to boost their performances and are also unaided by category retrieval cues [6]. Given that AD leads to a loss of semantic knowledge, the failure to demonstrate semantic knowledge for a particular item or concept has been shown to be consistent across test methods. Poor performance is also typically seen on confrontation naming tests and semantic categorization. Language discourse becomes increasingly filled with circumlocutions and overlearned phrases, accompanied by diminished meaning and spontaneity.

Visuospatial functioning tends not to be a prominent early feature of AD, but instead it regresses over the course of the disease. In particular, visuoconstructional deficits may be apparent on the Clock Drawing task and on complex copying tasks using drawing or blocks. A hallmark indicator of AD is the patients' tendency to perform their copy of a design extremely close to, touching, or on top of the stimulus item. Additionally, visuoperceptual and visual orientation abilities may become disturbed over time.

The neuropsychologist should utilize a battery of assessment measures that are sensitive to the cognitive deficits seen in AD and capable of distinguishing between age-related cognitive decline, MCI, AD, and other forms of dementia. Additional evidence of episodic memory impairment may be gathered from word list memory tasks, which can help identify deficits in encoding, storage, and retrieval. Combined visuoconstructional and visual memory tasks may be used which require the patient to copy shapes and then to recall those shapes after a delay, both from memory and with recognition cues [7]. A diverse range of skills may be assessed by administering a Clock Drawing task, including planning, visual attention, spatial orientation, and graphomotor control. Finally, since many patients with dementia have never undergone previous neuropsychological assessment, an estimate of premorbid IQ may be obtained by administering a word list reading task, such as the Wechsler Test of Adult Reading.

Currently, there are no other evidence-supported treatments for AD; however ongoing research aims to find disease-modifying treatments. Consensus statements have pointed to a multifaceted approach for conquering AD, using a combination of drugs to target a number of factors associated with the disease process, including Aβ deposits, NFTs, inflammation, immune dysregulation, and insulin resistance. Recent breakthroughs include results from a phase II clinical trial of IVIG, an immunotherapy agent, which was found to stabilize cognition and functioning, in a small sample of AD patients, for three years. Another promising finding came from a pilot clinical trial of an intranasal insulin therapy for AD and a-MCI in which participants that underwent treatment experienced memory improvement and/or maintained their current level of overall cognitive and functional performance.

Additionally, Alpha GPC, phosphatidylserine, Huperzine A, and choline show promise as nutraceutical agents for enhancing cognitive performance and slowing cognitive decline. Alpha GPC, also known as L-Alpha Glycerylphosphorylcholine, a naturally occurring form of choline, acts as a parasympathomimetic acetylcholine precursor and has shown promise in improving cognitive symptoms related to AD, vascular dementia, and multi-infarct dementia. Phosphatidylserine is a widely abundant anionic phospholipid in the human body and has been shown to improve age-related cognitive changes. Huperzine A has been linked to improved memory performance in elderly people with benign forgetfulness, as well as patients with AD and vascular dementia. Cholinesterase inhibitors have been shown to have neuroprotective properties in patients with mild as well as moderate-to-advanced AD [8].

The application of translational models, such as through animal and cell research, has helped identify certain processes and elements that may deter the neuropathogenetic

progression of AD. Research has begun to explore nonpharmaceutical interventions through translational models that may reduce toxins and prevent cell loss including apoptosis. In other words, once applications of interventions on animals or cells are deemed successful, they can be translated or applied to human participants. Laser light therapy is one such intervention, and animal studies using infrared light treatment have documented positive results in mice with traumatic brain injury. Stimulation of human mitochondrial processes and cell proliferation due to laser irradiation have also been demonstrated. More recently, researchers revealed a significant reduction of Amyloid-B aggregates in neuroblastoma cells that were irradiated with intense 670 nm laser light, leading the authors to suggest that their approach might inspire a practical therapy for AD. Ultimately, the most successful model of treatment for AD will likely include early detection and control of physical factors, followed by application of multifaceted, disease-modifying interventions to prevent the early and continued loss of neurons and to reduce the toxins that result in further cell deterioration [9].

Changes in personality and behavioral disturbances affect most patients with AD and can range from disinterest and apathy to agitation, affective disinhibition, and restlessness. Specific behaviors can be difficult to manage, such as aimless wandering, emotional outbursts, stubbornness, paranoia, hallucinations, and depression. Behavioral interventions can complement medication management and include creating a structured, safe, low stress environment, promoting regular sleep and eating habits, minimizing unexpected changes, and employing redirection and distraction.

Since ADLs such as self-care, personal hygiene, and dressing tend to worsen with the progression of the disease, patients with advanced AD require a greater level of caretaker commitment. Caregivers should be alerted to the challenges they will face as the disease progresses and be provided with appropriate coping skills, training, and interventions, through support groups and individual therapy. When at-home care is no longer an option, families will face the decision of placing their loved one in an assisted-living facility. Caregivers should not make this choice in isolation; mental health practitioners can help provide information and allow for the processing of the emotional weight of the decision and any mixed emotions of guilt, hurt, anger, and loss.

Considering that IADLs also decrease in AD, issues such as management of medical decisions, financial affairs, and cessation of driving will also emerge. When the patient is no longer able to perform basic math calculations, securing a financial advisor to oversee assets is often recommended. When insight becomes limited and memory is significantly compromised, medical decision-making and medication management may also need to be shifted to the hands of a caregiver. Pursuit of guardianship and capacity evaluations are not uncommon, especially when estate and legal issues need to be addressed [10].

Preventative interventions

AD is believed to emerge as the result of a complicated interplay of genetic, environmental, and lifestyle factors. Due to this complex process, it is difficult to pinpoint a definitive prevention strategy; however, there is mounting evidence that modifying certain lifestyle factors may lower the risk of developing AD. There is data to suggest that aerobic exercise may improve cognition and serve a protective role in healthy older adults by inducing neuroplasticity in areas of the brain associated with episodic memory. Additionally, physical activity has been found to improve scores on cognitive and functional measures in individuals with MCI and dementia [11].

As cardiovascular risk factors, such as diabetes, hypercholesterolemia, and hypertension, has been found to be associated with AD, it is hypothesized that preventing or managing these conditions may decrease the likelihood of developing AD. Research has shown that healthy eating, specifically adhering to a Mediterranean diet, correlated with both a lower risk of cardiovascular disease and AD. While there is ongoing research investigating the effects of various vitamins and dietary supplements in preventing AD, as of yet, clinical trials have not been able to prove their effectiveness.

In addition to maintaining physical health, engagement in cognitively stimulating as well as social activities seems important for promoting healthy brain functioning. Investigators have found that older adults who frequently participate in mentally demanding

activities have decreased odds of developing AD. Formal interventions involving cognitive training and time spent engaging in physical, cognitive, and social activities have been associated with a lower risk of developing dementia in healthy older adults, especially for individuals who participated in two or three of these endeavors [12].

Conclusion

Alzheimer's disease (AD) is an increasingly common condition with projected increased incidence rates in the population. Fortunately, research geared towards enhancing disease-modifying and preventative interventions is gaining momentum. Neuropsychological evaluation continues to play a critical role in early detection and differential diagnosis of normal aging versus MCI and the various types of dementia. Health care practitioners can offer strategies and support for patients, as well as their families and caregivers, related to the disruptions that AD has upon daily functioning. As researchers continue to make strides in our understanding of the disease, it is imperative for clinicians to remain abreast of the dementia literature in order to assist patients in obtaining the most effective care.

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