CE

Alzheimer Disease

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ABSTRACT

Alzheimer disease (AD), a progressive neurodegenerative disorder that affects cognition and behavior, has a clinical duration of approximately 8–10 years. It affects families, not just the individual. By 2050, more than 100 million individuals will be affected by AD worldwide. Memory impairment is the most common presenting symptom; however, others may present atypically. Thus, it is imperative for providers, especially those in primary care, to be able to recognize, diagnose, and manage this patient population. There are currently no disease modifying therapies; however, treatments that can ameliorate symptoms are available.

Keywords: Alzheimer disease, biomarkers, dementia, diagnosis, management

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Dementia is a clinical syndrome of progressive cognitive impairment and functional decline. Worldwide, there are approximately 47 million people with dementia, of whom 5.5 million are in the United States.[1] This number is expected to rise to 75 million people globally by 2030 and estimated to triple by 2050.[2] The estimated cost of caring for dementia patients in the United States alone is more than $230 billion and rising.[1]

The most common cause of dementia is Alzheimer disease (AD), the sixth leading cause of death in the United States. AD has a long preclinical and prodromal phase (up to 20 years) and an average clinical duration of 8–10 years. Currently no treatments are available to stop, slow, or reverse the progression of the disease process.[3]

ETIOLOGY AND RISK FACTORS

The risk of developing AD is multifactorial. Preventable risk factors include type 2 diabetes, hypertension, smoking, sedentary lifestyle, obesity, and head injury. The nonpreventable risk factors are age and genetics. For genetics, the biggest culprit is the e4 allele gene for apolipoprotein E (ApoE), which is present in 60% of individuals with AD. Compared with noncarriers of e4 gene, 1 e4 allele triples the risk of AD; and the risk of AD increases 7-fold in individuals homozygous for the e4 allele.[4] There are other less prevalent genes and familial tendencies that may cause AD. Overall, more than 20 genetic loci have been associated with AD risk.[5]

This CE learning activity is designed to augment the knowledge, skills, and attitudes of nurse practitioners and assist in the diagnosis and management of Alzheimer disease (AD).

At the conclusion of this activity, the participant will be able to:

A. Identify preventable and nonpreventable risk factors of AD
B. Describe specific diagnostics used to diagnose AD
C. Evaluate pharmacological interventions for AD symptom management

The authors, reviewers, editors, and nurse planners all report no financial relationships that would pose a conflict of interest.

The authors do not present any off-label or non-FDA-approved recommendations for treatment.

This activity has been awarded 1.0 Contact Hours of which 0.25 credits are in the area of Pharmacology. The activity is valid for CE credit until April 1, 2020

PATHOGENESIS

The core neuropathologic findings of AD are extracellular amyloid plaques, intracellular neurofibrillary tangles (NFTs), synaptic deterioration, and neuronal death. The amyloid cascade hypothesis suggests that the aggregate of amyloid plaques interferes with synaptic activity and initiates a series of downstream effects that cause inter- and intraneuronal dysfunction and ultimately cell death.[4]

Amyloid Plaques

All amyloid plaques contain β-amyloid protein (Aβ). Aβ is an amino acid peptide formed by proteolytic cleavage of APP by β- and γ-secretase. The main products of this cleavage are $A\beta_{1-40}$ and $A\beta_{1-42}$. A relative surplus of $A\beta_{1-42}$ predisposes toward amyloid aggregation into oligomers and fibrils that assemble into amyloid plaques. However, several lines of evidence indicate that amyloid plaques may not be the only contributing factor of AD.[6]

NFTs

Tau is one of the proteins involved in microtubule assembly. It is an essential component for normal axonal growth and neuronal development. Helical filamentous NFT are formed by hyperphosphorylated tau proteins that are deposited preferentially within neurons of the mesial temporal lobe (especially hippocampus), lateral parietotemporal region, and the frontal association cortices. The correlation between location, density of tau NFT, and the symptoms and severity of AD dementia are suggestive of the critical role NFT plays in the pathophysiology of AD.[6] As per the amyloid cascade hypothesis, the pathological alterations of tau are downstream events from Aβ deposition, but studies show that tau can act independently of Aβ to cause neurodegeneration. Therefore, it is plausible that tau and Aβ act in parallel pathways, causing AD and enhancing each other's toxic effects.[5]

Neuron and Synapse Loss

In AD, Aβ plaque causes death of neurons in the nucleus basalis of Meynert, which results in decrease in the synthesis and release of acetylcholine (Ach), along with an increase in activity of acetylcholinesterase, impaired muscarinic acetylcholine signaling pathways, and a decrease in cholinergic signaling and function. These changes indirectly disrupt *N*-methyl-D-aspartate receptor (NMDA) activity, which results in glutamate neurotoxicity. Because the plaque is concentrated in the basal ganglia, parts of temporal lobe and neocortex, memory, and executive function are affected.[7] Loss of median raphe and locus ceruleus neurons in the brainstem leads to deficits in serotonin and norepinephrine, respectively. In AD, dysphoria and insomnia are caused by abnormal cerebral serotonergic and adrenergic activity.[4]

DIAGNOSTIC CRITERIA

The clinical syndrome that manifests the AD pathophysiological process is referred to as AD dementia.[8] The first diagnostic criteria for AD dementia, established in 1984, had a sensitivity of 81% and specificity of 70%, were revised in 2011 by a workgroup appointed by the National Institute on Aging and the Alzheimer's Association.[8,9] It is intended for the use of both specialists who can acquire biomarkers (structural and functional imaging, cerebrospinal fluid analysis [CSF], and amyloid positron emission tomography) and neuropsychological testing and for general providers who may not have these tools readily available.[10] The revised diagnostic criteria for AD dementia acknowledges that multimodal biomarker approaches increase the pathophysiological specificity of the diagnosis; however, it does not advocate the use of biomarkers for routine diagnostic purposes at this time. Thus, clinical signs and symptoms remain the cornerstone for the diagnosis of AD dementia.[9]

The criteria for dementia require that the presenting symptom(s) (cognitive and/or behavioral) cannot be explained by any other medical, neurologic, or psychiatric condition; there is functional impairment; and the behavioral or cognitive impairment involves at least 2 of the following domains memory; executive function; visuospatial abilities; language; and behavior, personality, or comportment.[9]

To diagnose probable AD, the following must be met: meets dementia criteria; onset is insidious and progression is gradual (over several months to years); evidence of cognitive worsening either by