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Major review

Vision function abnormalities in Alzheimer disease

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ABSTRACT

Alzheimer disease (AD) is a progressive, age-related debilitating condition that is a growing public health problem in the developed world. Visual system abnormalities in AD were recognized in the early 1970s, but were initially considered to be of strictly cortical origin. Studies in the past 20 years reveal that all parts of the visual system may be affected, including the optic nerve and the retina. Some aspects of this involvement are still not well understood and are the subjects of intensive research. We summarize and focus on findings that may be of more practical interest to the ophthalmologist.

1. Introduction

Alzheimer disease (AD) is a progressive, age-related, debilitating condition and a growing public health problem in the developed world. This most common form of dementia has two forms: early onset and late onset (International Classification of Diseases, 10th Revision). The early-onset form of the disease, diagnosed before the age of 65 years and accounting for ~4% of all cases,[1] is caused most often by mutations in three genes (amyloid precursor protein [APP], presenilin 1, and presenilin 2) and is often inherited in an autosomal-dominant pattern.[25,303] In the late-onset form, most cases do not have a clearly identifiable Mendelian pattern. Recent studies, however, confirm the presence of strong genetic risk factors, such as the inheritance of the ε4 allele of the APOE4 gene, both for the early-onset and the late-onset form of the disease.[84,186] Presently, no effective treatment is available and the median life expectancy is between 7 to 10 years for patients diagnosed in their 60s and early 70s, or less if they are diagnosed later.[319]

Changes in the visual system associated with AD have been of interest for many years, with extensive reviews available covering different aspects of the problem.[117,130,143,155,197,295] We summarize the accumulated evidence with an emphasis on vision changes that could be of

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practical importance to physicians. We evaluate which vision symptoms may appear early during the development of the disease, and, therefore, could have a diagnostic and perhaps predictive value, and consider the potential for certain tests to be diagnostic instruments.

2. Epidemiology and public health importance

The prevalence of dementia in North America in people over age 60 years is about 6.4% of the population, and approximately 70% of those are attributed to AD.[74] The reported incidence for North America is 10.5 per 1,000. The estimated number of Americans suffering from AD is 5.4 million, including 5.2 million people aged 65 years and older and 200,000 under the age of 65 years.[1] Women are more likely than men to develop dementia at any given age. Presently, almost two-thirds of U.S. Alzheimer patients are women.[1] African Americans and Hispanics are more likely than whites to have AD and other dementias. By 2050, the number of people aged 65 years and older with AD may triple to a projected 11 to 16 million, barring the development of medical breakthroughs affecting the incidence and prevalence of the disease.[1,74,237]

The burden for society is enormous. In the United States total payments for health and long-term care for people with AD and other dementias in 2012 are estimated at $200 billion. To this the contributions of unpaid caregivers should be added. For 2011, an estimated 15 million Americans (80% of whom are family caregivers) provided 17.4 billion hours of care to persons with AD and other dementias, time valued at nearly $210 billion.[1]

3. Definition and diagnostic criteria

The current definition was established in 1984 based on the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria.[194] According to these criteria AD can be diagnosed as definite, probable, or possible. Definite AD requires pathological evidence, and probable AD is the maximum level of certainty without pathological confirmation and requires a gradual onset and progressive decline in memory with involvement of at least one other cognitive domain.

Recently, the clinical definition of AD has undergone revision. Thus, the preclinical stage is now separated, for research purposes, into three stages: stage 1 (asymptomatic cerebral amyloidosis), stage 2 (asymptomatic amyloidosis + "downstream" neurodegeneration) and stage 3 (amyloidosis + neuronal injury + subtle cognitive/behavioral decline).[266] The diagnosis of mild cognitive impairment from AD is defined by two sets of criteria: 1) core clinical criteria that could be used by healthcare providers without access to advanced imaging techniques or cerebrospinal fluid analysis, and 2) criteria that could be used in clinical research settings, including clinical trials.[3] Finally, the diagnosis of dementia from AD has been redefined. Biomarker evidence is integrated into the diagnostic formulations for probable and possible AD dementia for use in research settings. These biomarkers include positron emission tomography scan or cerebrospinal fluid evaluation for level of amyloid beta and neuronal injury markers.[195]

4. Pathophysiology of the disease relevant to the visual system

Two major factors are thought to contribute to the pathogenesis of AD: excessive formation of soluble and insoluble amyloid beta aggregates and accumulation of neurofibrillary tangles (NFTs), the result of hyperphosphorylation and aggregation of the tau protein.

Amyloid beta (Aβ), a peptide of variable length (from 36 to 43 amino acids), is expressed in most tissues in the body. Functions of the peptide include activation of kinases, protection against oxidative stress, and regulation of cholesterol transport.[14,124,277] It is metabolized from the parent protein (the APP) mostly into $A\beta_{40}$ and $A\beta_{42}$. The ratio between the $A\beta_{40}$ and $A\beta_{42}$ in human plasma and cerebrospinal fluid is typically 9:1;[131] in plaques associated with AD the predominant isoform is $A\beta_{42}$, however, which is less soluble and has the propensity to form aggregates.[32,279] Since the original observation by Alzheimer of amyloid plaques, the role of deposited amyloid has been much disputed. The "amyloid cascade hypothesis" is that the initial pathology in AD is amyloid accumulation and that a series of other events, including tau pathology, finally lead to neuronal death. Originally, amyloid plaques were thought to be the trigger for downstream events, but more recently soluble Aβ species (rather than the insoluble plaque amyloid) appear more directly pathogenic. Thus different soluble Aβ oligomers have been nominated as the species triggering the rest of the downstream events.[102] The reason for the accumulation of Aβ has also been much disputed and current theories include over-expression or increased metabolism of APP resulting in increased Aβ (particularly Aβ42) production. Alternatively, there may be reduced Aβ brain clearance. All of these mechanisms may possibly occur in AD and it is possible that different mechanisms occur at different stages of the disease and different disease subtypes may be particularly associated with one mechanism. For instance, some rare early onset genetic forms of the disease may be associated with increased Aβ production,[208] whereas late onset disease may be associated with reduced brain clearance of Aβ.[193] Whatever the cause of Aβ accumulation, the result is local toxicity, synapse dysfunction, and, ultimately, neuronal cell death. Thus, the current understanding is that amyloid plaques, which represent insoluble Aβ aggregates, are a late biomarker of the disease. The deposition of amyloid plaques in the brain is correlated with normal aging and deposits are found in frontal, cingulate, and parietal areas, with primary sensory/visual areas relatively protected, although the level of deposition exhibits considerable variability.[243] In contrast, in AD compared with controls, amyloid deposits are more widely distributed, including the frontal, cingulate, parietal, temporal and occipital regions.[68]