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# Alzheimer's disease: A defining role for the optometrist

## Introduction

As we age, we hope to reach a ripe old age and a live a long life with great memories and worthwhile accomplishments. We plan for retirement, our life savings ready to spend on our golden years. None of us are ready to face failing health and dementia as a reward for our hard work and frugal saving. Still, the staggering and exponential increase in the prevalence of Alzheimer's disease (AD) in our modern times almost belies the reassurance that this disease is not a part of natural aging. The prevalence of the disease doubles every five years in adults past the age of 65 — a tragic and ironic statistic of longevity. The current estimates are that an astounding 5.2 million Americans battle AD in 2014.[1]

There is hope. As a result of innovative and dogged research, we are now able to predict some of the risk factors and identify those who are at increased risk for developing this disease years — almost decades — before the patient displays the characteristic memory loss and dementia. Now more than ever, we have a window during which we can increase our symptomatic vigilance, start the available treatments earlier and, perhaps, even better focus our research.

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## The two types of Alzheimer's disease

The disease shows two distinct peaks of age at onset that correspond to the genetic and the interplay of genetic and environmental etiologies of the disease. The first type, known as early-onset AD typically affects younger people, usually before the age of 60. This type of AD runs in families and is mostly dominantly inherited. Several chromosomes have already been identified that contribute significantly to early-onset AD.[2, 3, 4] These genes are located on chromosome 1, 14 and 21 in families that show the early-onset disease.[2, 3, 4] The mutations affect amyloid precursor protein, presenilin 1 and presenilin 2, which, in turn, affect the production and deposition of amyloid-beta peptides that are known to build up in neuronal cells preventing them from performing their essential functions.[5, 6, 7, 8] Although genetic testing is available to patients who show signs and symptoms of early-onset AD and have a positive family history for the disease, there is no cure.[9] Prenatal testing is also available to patients who carry the genes providing us with a glimpse of the generational impact of the disease.[9]

Another group of people that are affected by the disease at a young age are adults with Down Syndrome. Adults with Down Sydrome (Trisomy 21) inherit an additional amyloid precursor gene from the extra chromosome 21, and it is the expression of this gene that is associated with the higher level of AD in this population.[10] AD and Down Sydrome have a 75% comorbidity that often presents before the age of fifty.[10, 11]

The second onset peak of AD occurs many years later. While many known contributors and risk enhancing factors have been identified, no single cause has yet been implicated. This group generally has no known familial or inherited factors. The strongest genetic risk factor is associated with the apolipoprotein E gene (APOE). It is located on chromosome 19 across 3 alleles and has a strong association with AD, vascular dementia and atherosclerotic disease.[12] This gene is predictive but not determinative of AD and not all patients with AD carry this gene.[13] A combination of epigenetic, environmental and vascular factors, in addition to the APOE gene and a few other identified candidate genes, seem to play a more significant role in the development of late-onset AD.[9, 14] Genotyping for APOE is commercially readily available, but not clinically as useful. Its best application is use as a research marker.[15]

## The risk factors associated with Alzheimer's disease

The risk enhancing factors for late onset AD seem to be mostly acquired during midlife.[9, 16, 17] Peripheral atherosclerosis, cerebrovascular disease and hypertension, type 2 diabetes and obesity feature prominently in the high risk category.[18, 19, 20, 21] Keeping fit and healthy lowers the risk. Physical activity improves cognitive function and reduces the overall dementia in patients who have the disease.[22] A higher risk can also be acquired accidentally. A history of brain trauma involving loss of consciousness significantly increases the risk.[22, 23]

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Active smoking, the severity and length of smoking, second-hand smoke, air pollution and the exposure to organo-chlorine pesticides carry a higher risk.[17, 26, 27, 28] This is true especially if the APOE gene is also present in the patient. Organo-chlorine pesticides are banned in North America; however, eating imported foods can still expose us to contaminated food, in addition to exposure from a variety of unintentional sources that build up in our bodies over time. Some medicated lotions, such as Lindane, are still prescribed for the treatment of lice and scabies. This chemical is easily absorbed through the skin contributing to cumulative CNS build-up.[29]

There are a multitude of environmental and situational factors that further predispose and aggravate AD. People who are isolated in their homes or living in a small space are also associated with increased risk.[30]

## The diagnosis of Alzheimer's disease

During life, the diagnosis of AD is generally clinical. The DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) requires three criteria to be met. The first is that the diagnostic criteria for a minor or major neurocognitive disorder is met, the second is that the onset is insidious and function gradually declines. The third requires that the diagnostic criterion for probable AD is met. This would include a decline in memory or learning based on trials, a steady decline and that there are no other indicators for other diseases that might cause the cognitive decline.[10]

## The significance of sleep in Alzheimer's disease

One of the earliest indicators that AD is incipient, within two years, is disrupted night sleep with daytime fatigue that

requires hypnotics as treatment in patients aged 50 years and older.[31, 32] The circadian dysfunction that occurs with AD is a well-known and frequent aspect of the disease.[33] Patients show more symptoms of dementia starting in the afternoon and evening, known as *sundowning*.[31] Amyloid-beta concentrations rise and fall diurnally and poor sleep and sleep apnea has been linked to the risk of development of cognitive impairment.[34] In turn, the resultant hypoxia is responsible for further cerebral amyloidogenesis and tau phosphorylation.[35] Amyloid -beta levels are known to increase in mice that are experimentally sleep deprived.[33]

Treating sleep apnea syndrome with continuous positive airway pressure (CPAP) significantly slowed cognitive decline in a study group over a three-year period and suggests that intervention of the at-risk population could be helpful.[35] The cholinergic donepezil is used to prevent memory loss in patients with AD, but one of its other benefits is that it improves obstructive sleep apnea index and oxygen saturation which suggests that cholinergic transmission influences breathing regulation in this population.[37]

## How Alzheimer's disease affects the senses

AD affects all the senses. Loss of hearing is an early marker for dementia, while the loss of the sense of smell is predictive that mild cognitive impairment is converting to AD with 85.2% specificity.[38] Difficulty recognizing and identifying odors is particularly challenging as the disease progressively affects higher cognitive function.[38] The sense of vision is emerging as an important and significant factor and predictor.

## The role of Amyloid Beta and Tau protein

There is much discussion amongst researchers about the role of the histologic buildup of characteristic plaques consisting of amyloid beta peptides and Tau protein neurofibrillary tangles within the brain. Many research projects are focused on these particular markers as significant in the prevention and treatment of the disease. The senile plaques and tangles are histologically present in the post mortem evaluation of patients with AD, though not all patients that show plaques and tangles had dementia during life. The presence of plaques and tangles affect the normal functioning of the cholinergic neuronal brain cells and, as a result, produce reduced acetylcholine. The reduction in acetylcholine is what inevitably creates the memory loss and the typical behavioral symptoms. When associated with AD, the pathological changes that occur due to the accumulation of amyloid can be detected in the brain as early as 15 years before the onset of dementia, while the evaluation of the cerebrospinal fluid shows changes as early as 25 years before onset of the disease.[39] In this long period between first detecting the plaques and the onset of dementia, patients are asymptomatic.

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## Detection of plaques and tangles in the living patient

Detection of plaques and tangles while the patient is alive can be helpful in the diagnosis of the disease. Utilizing positron emission tomography (PET) scan techniques in conjunction with the newer FDA approved amyloid PET tracers is very effective but expensive and not routinely done for clinical care. Magnetic brain resonance imaging (MRI) is a far more accessible method to evaluate brain atrophy. The MRI can demonstrate diffuse atrophy, plaques and hippocampal volume, all of which contribute to the qualitative assessment, diagnosis and prognosis of the disease for the patient.[40]

Eye care professionals have a significant and growing role to play, in the early identification of this devastating disease. Probably one of the most exciting recent research contributions in the early detection and diagnosis of AD is underway at Cedars-Sinai in Los Angeles. The collaborative efforts of researchers across several specialties at Cedars-Sinai are developing a non-invasive imaging technique to detect amyloid plaques, like the ones in the brain, in the retina of the eye.[41, 42]

Researchers have found that these plaques could be detected after a systemic administration of curcumin to an AD mouse model. It was also discovered that the plaques could be detected earlier in the retina than in the brain and deposition of the plaques followed the development of the disease.[41, 43]

Another exciting development is that researchers found that in the mouse model of AD, beta amyloid deposits clear when these mice are vaccinated nasally with glatiramer acetate. Glatiramer acetate is also known as Copaxone, a synthetic co-polymer, and is already extensively and safely used in humans for vaccination against the exacerbating-relenting type of multiple sclerosis, and also in the treatment of several other autoimmune diseases.[44, 45]

## The structural and functional changes in the eye and vision

While we await the launch of the new era of non-invasive detection, we are still able to detect and quantify the visual perceptual and ocular functional/structural changes that accompany AD. We are able to identify for our patients risk factors that increase the likelihood of future development of AD. What we do with that information, how we educate our patients and the public, how we monitor our patients over the next two or three decades of their lives depends on our committed vigilance and our determination to eradicate this scourge from the face of the earth.

One of the most non-invasive and currently only experimental methods to screen for pre-clinical AD is to measure the speed at which the pupil responds to a bright flash of light. Both the speed and latency of the pupillary response are diminished in patients with AD.[46, 47] Poor pupillary response would lead to concern over cataract formation. Cataracts are found in conjunction with AD, but not solely for the reason of increased exposure to harmful rays as we would expect. An additional method of cataractogenesis is by beta amyloid deposition into the cortex of the intraocular lens. These have been termed *equatorial supranuclear cataracts*.[48]

Associated with retrograde ganglion cell death that starts in the brain, the optic nerve soon shows associated damage. Typically, there is a pale increase in the size of the optic cup with vertical elongation of the cup. The effects of AD on the optic nerve look similar to primary open angle glaucoma (POAG) and can be challenging to differentiate but changes from AD are associated with perceptual changes or dementia that is not associated with

POAG. To confound the diagnosis, the two diseases commonly occur together and visual field defects are progressive in both conditions. Another important differentiator is that AD typically does not cause increased intra-ocular pressure.

As with glaucoma, damage to the optic nerve is more significant with smaller optic nerves and with advancing age, where the mean annual normal fiber loss is already in the region of about 4000 fibers per year.[49] There is diffuse nerve fiber layer thinning, with additional thinning particularly in the superior-temporal area of the nerve, that can be demonstrated by measurement with ocular coherence tomography (OCT).[50] Surrounding the optic nerve, peri-papillary atrophy can be seen, the cerebral and optic nerve blood flow anomalies that commonly accompany the disease responsible for the characteristic changes. The vascular supply to the choroid declines and the choroid thins significantly.[51, 52, 53]

The retinal vasculature also shows telltale signs. Amyloid beta deposition in the veins can cause the vessels to constrict noticeably.[54] ( Figure 1) Amyloid beta also deposits within the neuro-retina and causes apoptosis of the retinal ganglion cells in a way that is reminiscent of induced cell death in animal models of glaucoma.[54, 55] Interestingly, the maculas of patients with AD show significantly less macular pigment when compared to healthy controls, and the disease may have potential links to age-related macular degeneration.[56, 57, 58] Amyloid beta oligomers have been identified within drusen associated with age related macular degeneration and weekly vaccination with Copaxone has been shown to reduce the area of the drusen.[59, 60]

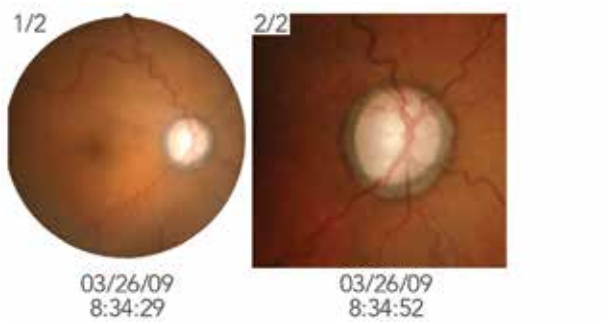


**Figure 1:** The image depicts the vertical elongation of the cup and pallor the of the optic nerve in a patient with Alzheimer's disease. Peri-papillary atrophy and narrowed vasculature is also present.

## The visual variant of Alzheimer's disease

The disease itself may present more posteriorly in the brain. When this occurs, this variant can present with an awareness of visual change as experienced by the patient, without any signs of dementia.[61] This is also known as posterior cortical atrophy.

When the disease then primarily affects the visual cortex, the changes that occur can be divided into two major constellations of events describing the basic properties of vision and the associative aspects of vision.

The associative aspects of vision usually deteriorate first. The loss of visual-memory starts early, errors on the Benton Visual Memory test has been shown to indicate an increased risk to develop AD fifteen years before dementia leads to a diagnosis.[62, 63] Visio-spatial disorganization is very common. The spatial disorientation and difficulty with motion detection commonly leads to abandonment of driving.[65, 66]) Patients with visual-spatial disturbances have great difficulty with the Clock Dial Test, especially if requested to place the hands at the "ten after eleven" position.[64] (Figure 2)

**Figure 2:** The clock dial test shows the typical visuo-spatial disorganization of a patient with Alzheimer's disease.

Then, the basic or apperceptive properties of vision deteriorate.[64] Color vision is affected, leading to difficulty with blue hues especially.[67] Depth perception decreases. Saccades become dysmetric and saccadic initiation is prolonged.[64] Near acuity deteriorates and reading becomes affected by the crowding phenomenon.[68] Alexia and agraphia are common findings in AD.[64,65]

Visual field loss, particularly general depression, and often with defects in the inferior hemi-field are the most common, and can present with or without visual neglect.[69, 70] The primarily magnocellular pathway loss is expressed in the deficits in frequency doubling visual field testing and significant decrease in contrast sensitivity.[71]

## Conclusion

All these changes may precede the onset of dementia. Once dementia sets in, the cognitive and behavioral decline is relentless. While the process can be somewhat delayed by medication, typically, death occurs within about seven years. The familial type or Early-onset AD has a longer duration than the sporadic disease.[72]) The doctor of optometry has an important role to play in the prevention and early detection of the ocular and visual changes that herald the onset of AD. We have an even more critical role to play in the education of our patients and the public about the preventable risk factors that are associated with AD.

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