

# Alzheimer's disease: Visual system review

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## KEYWORDS

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## Abstract

**BACKGROUND:** Ten million baby boomers in the United States will get Alzheimer's disease. Optometrists can benefit from understanding the impact the Alzheimer's disease process has on the visual system. This can result in more effective management of the condition and in more effective communication with members of the Alzheimer's disease multidisciplinary team.

**METHODS:** This is a review of the literature but by no means a completely exhaustive review. Alzheimer's disease is a complex disease. A rapidly expanding body of knowledge covers multiple disciplines.

**RESULTS:** The visual system shows deficits early in the degenerative process of Alzheimer's disease. Biomarkers through the visual system such as nerve fiber deficits, lens opacities, and functional losses in the magnocellular pathway, such as contrast sensitivity and temporal processing, may prove to not only help detect Alzheimer's disease early but also detect it before there are the classic cognitive and memory losses.

**CONCLUSIONS:** The effects of Alzheimer's disease are devastating. Optometrists, as primary care clinicians, can make critical contributions in the diagnosis, treatment, and management of this neurodegenerative disease.

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The 2000 census of the United States indicated there were 4.5 million people in the United States with Alzheimer's disease (AD). Current numbers are approaching 5.1 million, and this number is expected to reach 13.2 million by the year 2050.<sup>1</sup> It is the sixth leading cause of death in the United States, surpassing diabetes.<sup>2</sup> AD is estimated to cost Americans \$148 billion a year both in direct costs and indirect costs.<sup>3</sup> Medicare expenditures for AD were \$31.9 billion in 2000 and are projected to be \$49.3 billion in 2010.<sup>4</sup> The amount spent by Medicaid to provide residential care for recipients with dementia is expected to increase 80 percent, going from \$18.2 billion to \$33 billion in the year 2010.<sup>4</sup> Early diagnosis and treatment are critical

if there is to be any hope of mitigating the devastating financial and social impact of AD.

AD impacts visual function early in the course of the disease and functional losses correlate with cognitive losses. The initial pathology of Alzheimer's disease may originate in the visual association area as evidenced through the findings of McKee et al.<sup>5</sup> in their studies of autopsied brains in the Framingham Heart Study. They found that in the visual association area of more than 50% of those who were considered cognitively normal there were no memory impairments, but there were findings of beta amyloid and neurofibrillary tangles, the presence of which are associated with Alzheimer's disease. In some of these same cognitively normal cases there was an absence of such pathology in the hippocampus area, which processes memory. In essence, there was pathology in the visual association area but not in the hippocampus area in some participants. The researchers hypothesize that instead of starting in the brain's regions that process memory, such

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as the hippocampus, AD may actually start in the portion of the brain that integrates visual function with other areas of the brain, the visual association area. Visual function loss other than acuity may be the first indication of AD. Visual function losses in AD have many aspects in common with functional losses in other neurodegenerative processes affecting the eye, such as age-related macular degeneration and glaucoma.<sup>6</sup>

- In people with AD, contrast sensitivity deficits in the lower spatial frequencies are found,<sup>7</sup> motion perception, i.e., the ability to detect movement, is reduced,<sup>8-10</sup> there are visual field defects,<sup>11,12</sup> and color discrimination of blue, short wave length hues have been found to be reduced.<sup>13</sup>
- People with glaucoma have been shown to have decreases in lower spatial frequencies in contrast sensitivity, visual field defects,<sup>14</sup> deficits in the blue short wavelength color range,<sup>15</sup> and reductions in motion perception.<sup>16</sup>
- Age-related macular degeneration affects all frequencies of contrast sensitivity,<sup>17</sup> demonstrates color deficits across all wavelengths,<sup>18</sup> and decreases foveal detection of motion.<sup>19</sup>

## Glaucoma and AD

When patients with AD also have glaucoma, the course of vision loss related to glaucoma is much more rapid and aggressive.<sup>20</sup> It is estimated that glaucoma affects more than 3 million Americans, but only one half of those cases have been diagnosed.<sup>21</sup> The National Institutes of Health (NIH) reports that approximately 2.2 million Americans have had glaucoma diagnosed with the prevalence expected to rise to more than 3 million cases by the year 2020.<sup>22</sup> Glaucoma is responsible for 9% to 15% of blindness in the United States<sup>23</sup> and is the leading cause of blindness among blacks<sup>21</sup> (blacks suffer blindness with visual acuity reduced to worse than 20/200 from glaucoma 8 times more frequently than whites<sup>24</sup>) and Latinos.<sup>25</sup> Those older than 60 years of any race are at greater risk of glaucoma development,<sup>26</sup> and it is estimated that 8% of those over the age of 80 have elevated intraocular pressure (IOP).<sup>26</sup>

Cholinesterase inhibitors (ChEI) are commonly prescribed for the treatment of AD, and they also affect IOP by lowering it.<sup>27</sup> This is a positive side effect of the pharmaceutical interventions for AD, as this side effect may also be protective for retinal ganglion cells.<sup>28</sup> ChEI have been approved for the treatment of AD and are generally the first line of treatment for mild, moderate, and severe AD.<sup>29</sup> There are primarily 3 U.S. Food and Drug Administration (FDA)-approved ChEI for the treatment of AD in the United States: donepezil (Aricept; Eisai Inc., Woodcliff Lake, New Jersey), rivastigmine (Exelon; Novartis Pharmaceuticals, East Hanover, New Jersey) and galantamine (Razadyne; Ortho-Mcneil-Janssen Pharmaceuticals Inc., Titusville, New Jersey).<sup>29</sup> Estermann et al.<sup>27</sup> showed an 8.8% reduction of IOP in 63 eyes of those newly

diagnosed cases of AD when patients were placed on donepezil (a selective form of ChEI in an oral dose). Donepezil was also shown to have a neuroprotective effect in retinal ganglion cells exposed to glutamate toxicity in rats, both in vivo and in vitro with an orally administered dose.<sup>28</sup> Topical rivastigmine, a selective carbamate-type ChEI, was shown to have a dose-dependent lowering of IOP in rabbits in an investigation by Goldblum et al.<sup>30</sup> They found that this selectivity inhibits the isoform of the enzyme that is almost exclusively found in the central nervous system. Rivastigmine, with 1 topical administration, decreased IOP 23% in a concentration of 5%, 20% at 2% concentration, and 15% with a 1% concentration. The effect was maintained upon measurement at 5 hours.<sup>30</sup>

Neuroprotective treatments used for AD also have implications for the visual system and may have an impact on glaucoma progression. In numerous double-blind studies, memantine has been shown to benefit cognition, function, activities of daily living, behavior, and global performance in those with moderate to severe AD.<sup>31-33</sup> Memantine is currently FDA approved for the treatment of moderate to severe AD and is available as Namenda (Forest Laboratories, Inc., New York, New York). Memantine has been investigated for the treatment of glaucoma. Treatment with memantine in glaucoma has been shown to slow down the progression of cell loss in the lateral geniculate nucleus in monkeys with glaucoma compared with those animals not treated in a study undertaken by Yucel et al.<sup>34</sup> Both AD and glaucoma affect the same visual pathways but start in different regions along the neural pathway. AD may initially start in the visual association area, whereas glaucoma has its initial damage to the neural tissue in the optic nerve.

Glaucoma affects the lateral geniculate nucleus. There is shrinkage and change in the lateral geniculate nucleus neurons early on in the glaucoma disease process, which can be observed even before nerve fiber loss in the optic nerve.<sup>35,36</sup> A single case study of the changes of donated brain tissue in the visual cortex in human glaucoma undertaken by Gupta et al.<sup>37</sup> clearly found reductions in the autopsied tissue of a patient in the area below the calcarine sulcus compared with that of normal control autopsy tissue. This finding corresponded to the superior visual field loss that had been identified in the same patient before death. There are losses in all layers of the lateral geniculate nucleus but substantially more loss in the magnocellular layers.<sup>36,38</sup> The magnocellular pathway has its primary receptors in the retina, but the pathway itself extends to the primary visual cortex with lateral and retrograde connections that relay visual information related to achromatic functions, such as motion and contrast.<sup>39</sup> Deficits specific to the magnocellular pathway have also been identified in individuals with AD even in brain areas devoid of plaques and neurofibrillary tangles. The magnocellular pathway shows signs of significant cell loss in the primary visual cortex of AD individuals.<sup>40</sup> Amyloid plaques and neurofibrillary tangles have been identified in the cuneal and lingual gyri of participants with AD,

and these correlate with the incidence of functional visual field loss in AD participants.<sup>11</sup> In the lateral geniculate nucleus, the magnocellular layers have been shown to have plaques associated with AD.<sup>41</sup>

The IOP of the eye follows a circadian rhythm with increases at night.<sup>42,43</sup> Disruptions in the circadian rhythm have high prevalence in AD patients, with rates ranging from 12% to 25%.<sup>44</sup> AD is associated with changes in the suprachiasmatic nucleus, the nucleus primarily responsible for processing circadian functions.<sup>45,46</sup> The phenomenon of “sundowning” may be secondary to disruptions in the circadian rhythm of AD patients. *Sundowning* is a general term that has been used to describe a variety of symptoms, such as sleep disturbance, nocturnal delirium, and disorientation at the onset of darkness, night-time activity, and agitation.<sup>6,47</sup> Transgenic AD mouse models have been shown to have significant deficits in sleep function with disturbances in circadian rhythms.<sup>48,49</sup> The deficits were attributed to dysfunction in the cholinergic system, and the ChEI donepezil facilitates alertness but less so in the animals transgenic for AD.<sup>48</sup>

Sacca et al.<sup>43</sup> found greater fluctuation and range in IOP in individuals with glaucoma compared with healthy control individuals, as did Noel et al.<sup>50</sup> Studies by Liu et al.<sup>51</sup> also found that the larger the diurnal variation and fluctuation of IOP, the greater the risk for glaucoma. A possibility is that the fluctuation is not a risk factor but actually an early symptom of glaucoma, as the disease affects the optic nerve and the axons leading to brain structures processing circadian function. Light has a strong influence on the circadian system, and the timing and duration of exposure to daylight can impact circadian phases, melatonin suppression, physiological responses, and alertness.<sup>52</sup> Berson et al.<sup>53</sup> identified a previously unknown photoreceptor that was dissimilar to both rod cells and cone cells. These cells are retinal ganglion cells that directly innervate the suprachiasmatic nucleus and are reactive to light even when all synaptic input from rod cells and cone cells is blocked.

A recent study of nursing home residents found a higher rate of glaucoma among 112 residents with AD compared with 774 residents without AD. The diagnosis of glaucoma was based on visual field defects or optic nerve cupping. The rate was 25.9% for AD patients and 5.2% for the control nursing home group.<sup>54</sup> The conclusion was that the optic nerve may be less resistant to elevated IOP levels in AD. A retrospective review of records in a large glaucoma clinic found that 7 patients with ocular hypertension with normal visual fields and normal optic discs had glaucoma diagnosed within 1 year of an AD diagnosis. They found that among these patients, there was a more severe progression of glaucomatous optic neuropathy compared with other glaucoma or ocular hypertensive patients.<sup>54</sup> The Medicare diagnostic data of 54,232 patients with open-angle glaucoma along with an equal number of age-matched control participants covering a span of 12 years were reviewed by Ou et al.<sup>55</sup> They found that those with AD had a statistically significant greater risk of glaucoma development when compared with

the controls.<sup>55</sup> An additional study likewise found a higher rate of glaucoma among AD patients compared with non-AD patients. In their study of 172 patients with AD in Japan compared with 176 age-matched controls, Tamura et al.<sup>56</sup> found those with AD had a rate of glaucoma of 23.8% compared with only 9.9% of the age-matched controls having glaucoma. If there are 2 neurodegenerative processes such as glaucoma and AD affecting one of the major relay centers for visual function, it is easy to appreciate that the loss in function can be substantial. AD also affects the nerve fiber layer, giving indication that although they have different origins, some structures and functions are similar in the 2 neurodegenerative diseases.<sup>6</sup> Findings by Enzenauer and Bowers,<sup>57</sup> shortly after the approval of donepezil for the treatment of mild AD, indicated that the cholinesterase inhibitor may have a negative impact on the visual system. They reported a case of angle-closure glaucoma in a patient after the abrupt discontinuation of the ChEI, donepezil. They also discussed 3 additional cases of angle-closure glaucoma reported in the National Registry of Drug Induced Ocular Side Effects after the sudden discontinuation of the use of the ChEI, donepezil.

## Age-related macular degeneration and AD

Age-related macular degeneration is a leading cause of blindness in whites,<sup>23</sup> and, as with AD, is age related, has vascular influences, and results in apoptotic cell death.<sup>58</sup> Increasing numbers, size, and confluence of drusen is associated with an increased risk of choroidal neovascularization and geographic atrophy.<sup>59</sup> A study of surface retinal photographs was made of a sample of Icelandic white subjects. It was found that 5% of those between 50 and 59 had drusen, but at least 20% of those over the age of 80 years had dense drusen, with 10% of those over age 70 showing evidence of age-related macular degeneration.<sup>60</sup> The Beaver Dam study of more than 2,000 participants of a diverse racial heritage having serial retinal photographs found that for patients 43 to 86 years, there was an initial rate of drusen that was less than 1%; however, in the 75 and older age range, this rate was 6.6%.<sup>61</sup> Autopsy studies of 10 samples of retinal tissue obtained from all races with donor ages between 58 and 93 years indicated the presence of drusen in 100% of the tissue under histologic study.

A report from the Age-Related Eye Disease Study (AREDS) group indicated that there is a relationship between the severity of age-related macular degeneration and cognitive dysfunction in older patients.<sup>62</sup> Findings suggest that AD and age-related macular degeneration may have pathologic processes in common.<sup>63</sup> The deposits in the brain of AD and the deposits of drusen in the retina with age-related macular degeneration both contain amyloid beta.<sup>64-66</sup> Other components that are found both in AD-related deposits and drusen are proteins such as vitronectin, amyloid P, and apolipoprotein E.<sup>67</sup> Thinning of the retina in age-related macular degeneration is attributed to the atrophy of the photoreceptors.<sup>68,69</sup> The histologic

retinal studies in AD as well as the optical coherence tomography studies of macular thickness indicate that there may be retinal thinning in AD also.<sup>70</sup> The thinning may be related to cell death and apoptosis. Two studies have found decreases in the number of retinal ganglion cells of the maculae of individuals with AD compared with age-matched control individuals. Blanks et al.<sup>71</sup> found that there was a loss of retinal ganglion cells averaging 25% for individuals with AD. In a separate study, it was found that 4 of 9 retinas from those with age-related macular degeneration, but none of 9 retinas from control individuals, had amyloid beta proteins in the retina.<sup>72</sup> It was suggested that the presence of amyloid beta in lesions may correlate with the location of degenerating photoreceptors.<sup>72</sup> However, none of the individuals with age-related macular degeneration or the control individuals had a diagnosis of AD at death, and there were no studies of brain tissue performed on either group; therefore, there is no means of identifying the cognitive status or relationship to AD.

Apolipoprotein E (apoE) genotypes have been shown to be a risk factor for both AD and age-related macular degeneration, although some findings show apoE2 to be the risk genotype for macular degeneration and apoE4 the risk genotype for AD.<sup>73</sup> In animal models of both apoE2 and apoE4, both strains get pathology indicative of macular degeneration, but the apoE4 strains show the greatest severity and the stronger similarities to the age-related macular degeneration found in humans, with subretinal pigment epithelial deposits, drusen deposits, thickening of Bruch's membrane, and choroidal neovascularization.<sup>66,74</sup> Immunotherapy treatment targeting amyloid beta has been shown to reduce the volume of drusen and improve visual function in a mouse model of age-related macular degeneration.<sup>75</sup>

## Cataracts and AD

Cataracts are a normal part of aging. However, those with AD may have a risk for different types of cataracts than those without AD. Goldstein et al.<sup>76</sup> identified amyloid beta proteins in the cytoplasm of lens fiber cells in 4 lenses of those with AD upon autopsy and identified supranuclear equatorial opacities in 9 eyes of those with AD but not in the 8 eyes from control donors who did not have AD.<sup>76,77</sup> Cataracts also develop in mice transgenic for AD to a greater extent than wild-type control mice, but the cataracts are partially resolved with antioxidant treatment.<sup>78</sup> Growth factor receptors are functional only in the equatorial peripheral cells of human lenses,<sup>79</sup> making this area more vulnerable to cell proliferation that can induce opacities, not just in AD but in general. This is the only region of the lens that is mitotically active.<sup>80</sup> This mitotically active region is also the only portion of the lens that was found to have the ability to actively initiate small molecule transport into and through the lens.<sup>80</sup> This may make the equatorial region of the lens more vulnerable to cataract formation and in particular in those with AD. Higher concentrations of amyloid beta proteins were found in the aqueous of those with

AD than the aqueous of control participants.<sup>76</sup> It makes sense, therefore, that the excess of amyloid beta in the aqueous fluid would create greater opportunity of abnormal entry and transport into the equatorial region of the lens. A decrease in acetylcholine receptors and acetylcholine signal processing deficits have been put forth as contributing to AD pathology. The equatorial supranuclear region of the lens, in the absence of any pathology, is one of the few tissues and regions in the lens that has active acetylcholine receptors throughout life, even into advanced aging.<sup>81,79</sup> Interference with acetylcholine signaling has been postulated to be causative of cataracts and lens opacities, and that is why earlier ChEI therapies, such as echothiophate, in the 1960s and 1970s for glaucoma were discontinued.<sup>82,83</sup> An increased abnormality related to acetylcholinesterase signaling, as in AD, could give rise to increased risk of lens opacities and cataracts. The equatorial region of the human lens is dense in muscarinic acetylcholinesterase receptors with fewer such receptors more anterior in the lens. The additional pro-mitotic action of impacting muscarinic-specific receptors may accelerate the normal mitotic activity and transport function of the supranuclear equatorial region, disrupting the clear matrix with an overabundance of cells. This has been seen in animal primate models using the ChEI echothiophate and the muscarinic receptor antagonists, atropine and tolterodine, in rodents.<sup>84,85</sup> All 3 result in anterior polar cataracts.

The biomarker for AD of supranuclear equatorial lens opacities identified by the Goldstein group may be amplified with the use of ChEI. The side effect of drug-induced supranuclear equatorial cataract does not affect visual function when the ChEI are primarily muscarinic specific, such as with the ChEI used in several AD treatments, as the opacities are in the extreme periphery and do not affect acuity. Further, once the lens has been removed as a result of an age-related cataract, the epicapsular membrane remaining to hold the artificial intraocular lens no longer contains muscarinic receptors, so the potential for ChEI-induced opacities, or for that matter further AD-related opacities, is reduced or even eliminated.<sup>79</sup>

Although the neuroprotective drug memantine was originally approved for treatment of dementia and now is being investigated for use in glaucoma, the reverse is the case for the drugs acting on the cholinergic system. ChEI-type treatments had historically been used as treatment for glaucoma in the form of anticholinesterase drugs. The irreversible inhibitor of cholinesterase, echothiophate iodide (phospholine), was a standard of treatment in the 1960s<sup>86,82</sup> and worked remarkably well in reducing IOP. However, cataracts were a side effect of the treatment. Cataracts were also a side effect of the other anticholinesterase drugs of the era: demecarium (Humorsol) and isofluorophate (Floppy).<sup>82</sup> Echothiophate iodide is no longer used, as other more effective therapies were introduced that had fewer side effects. In a study of the ocular topical application of echothiophate iodide, it was found that with a 0.25% therapeutic solution for glaucoma there was a resultant 75%

to 80% plasma cholinesterase inhibition,<sup>86</sup> whereas a lower dose of 0.06% and 0.03% produced only a 35% to 40% inhibition. There is every indication that an ocular dose of ChEI produces a systemic effect, so it makes sense that a systemic dose would produce an ocular effect. Pilocarpine, which also acts on the cholinergic system, had been in common use as first line therapeutic intervention to lower IOP in glaucoma. Also, cataract is a side effect of the use of Pilocarpine,<sup>87,88</sup> but because it is a milder miotic with the action of a choline agonist rather than an choline esterase inhibitor, the rate and severity of cataracts is smaller.<sup>87</sup>

## Pupillary function and AD

The excessive mydriatic response to dilute tropicamide in AD has long been acknowledged,<sup>89-90</sup> but its practical application as a diagnostic biomarker for AD due to the difficulty of delivering a precise known quantity of eye drop has not been established.<sup>91</sup> This excessive reaction is related to cholinergic systems. Miotic drops such as pilocarpine, which constrict the pupil, also have an exaggerated response, further suggesting defective innervation in AD.<sup>92,93</sup> Recent work using a prospective longitudinal design followed participants who had an initial exaggerated response to mydriatics over a period of 2 to 4 years. They found that an exaggerated pupil response to mydriatics predicted a 3-fold risk of the development of clinically significant cognitive impairment, and when there was an associated ApoE4 genotype, the risk increased to 4 times.<sup>94</sup> Ten characteristics of pupil responses were used to compare normal age-matched control participants with those with probable AD, and it was found that all but 2 of the 10 characteristics were correlated with AD.<sup>95</sup> The maximum constriction acceleration and percentage of recovery were the best predictors. A factor in a recent study involving pupillary function and AD is the influence of ChEI treatment. The ChEI, donepezil, was shown to constrict the pupil with an average change from 3.9 mm to 3.6 mm.<sup>27</sup>

Further support of the deficits in pupillary response were established with a study that identified profound loss of neuronal structures in the Edinger-Westphal nucleus, one of the primary neural structures involved in pupillary response.<sup>96</sup> Recent work indicates the Edinger-Westphal pathology is primarily tau (tau is a biomarker of AD pathology),<sup>94</sup> much like the predominant pathology identified in the visual association area, Brodmann 19.<sup>5</sup> The Edinger-Westphal nucleus controls ocular accommodation through the ciliary muscle. The ciliary muscle contraction is mediated through muscarinic receptors, and the ciliary muscle contraction is what facilitates outflow of aqueous and the subsequent lowering of IOP.<sup>97</sup>

## Ocular AD-related histopathology

All 3 diseases of the eye associated with aging eventually affect the ocular pathway and neuroprocessing of visual signaling; cataracts affect the quality of entering light and

signal strength, age-related macular degeneration causes a breakdown of signal at the cellular level, and glaucoma acts primarily at the transport level in the optic nerve. With the degradation of neural signals in the visual system at the eye level, losses in neuroprocessing at the brain level are more profound. AD is characterized by senile plaques with the deposition of beta-amyloid accompanied by neurofibrillary tangles. A definitive diagnosis of AD occurs with identification of plaques and tangles at autopsy.

AD damages the lateral geniculate nucleus early in the disease process,<sup>41</sup> and glaucoma damages the lateral geniculate nucleus early in the disease process as well.<sup>98</sup> Shrinkage and change in the lateral geniculate nucleus neurons early on in the glaucoma disease process can be observed even before nerve fiber loss in the optic nerve with conventional histologic studies<sup>35,36</sup> and magnetic resonance imaging in vivo in humans.<sup>37</sup> Damage secondary to AD also occurs in the visual association cortex and other higher cortical areas, the primary visual cortex,<sup>99,40</sup> and visual association areas.<sup>5</sup> Additional studies have found deficits in the retinocalcarine pathway.<sup>100,101</sup>

Retinal ganglion cell degeneration of patients with AD was identified histopathologically by several groups.<sup>6</sup> Blanks et al.<sup>71</sup> examined 16 individuals with AD with an age range of 76 to 93 years. There were 19 normal individuals with an age range from 55 to 91 years. They found that within the ganglion cell layer, the cells having the largest diameter may have been preferentially affected in AD. Hinton et al.<sup>102</sup> utilized histopathologic studies on 10 individuals with AD and 10 age-matched normal individuals age 76 to 89 years. This study found 8 of the 10 participants with AD to have optic nerves that were significantly different in nerve fiber count compared with normal individuals. The level of AD severity or duration of illness was not documented. Sadun et al.<sup>101</sup> examined 3 eyes from AD individuals ranging in age from 76 to 89 years. In these retinas, there was degeneration of the retinal ganglion cells and axonal degeneration on examining the retrobulbar optic nerves. A greater frequency of degeneration occurred in the more posterior portions of the nerves. The implication was that the retinal ganglion cell loss may be secondary to retrograde axonal degeneration. The findings of Blanks and Sadun differ from the findings of Curcio and Drucker<sup>100</sup> who examined 4 AD eyes with an age range of 67 to 86 years as well as the eyes from 4 age-matched normal individuals. These individuals with AD had the disease for at least 4 years and had severe dementia, but there was no group difference with regard to the ganglion cells. Davies et al.<sup>103</sup> studied 9 AD and 7 normal eyes and also reported that there was no histopathologic evidence of differences in the retinal ganglion cells from the retinas of individuals with AD and the retinas of age-matched normal individuals.

## Retinal photographs and AD

Photographs are used to analyze retinal ganglion cell loss and cell function. Photographic images are used to measure

the degeneration of the cell's nerve fiber layer, an indirect method of assessing loss of cell function. The nerve fiber layer is made up of the individual cell axons. Histopathology methods rely solely on cell count with no mechanism to measure cell quality. Measuring the integrity of the cell fiber layer assesses loss in cell function that may actually occur before the loss of the cell itself. Photographic images also record optic nerve parameters such as depth, tilt, and vasculature, and the observer can determine readily which eye is under study and the orientation of the nerve itself. Identification of which eye and the orientation of the nerve, such as temporal versus nasal, is important when considering retrograde neural disease. All photographic studies have shown a difference in the nerve fiber layer in individuals with AD compared with normal individuals.<sup>6</sup>

Tsai et al.<sup>104</sup> photographed 22 AD participants and 24 normal age-matched participants. Five of the AD participants had nerve fiber loss compared with one of the control participants. The photograph images showed that there was a significant correlation in degree of segment optic nerve pallor and the duration of AD. Hedges et al.<sup>105</sup> studied the retinal nerve fiber layer by photographs in participants in various stages of AD. They found a greater amount of nerve fiber loss in individuals with AD ( $n = 26$ ) compared with age-matched normal individuals ( $n = 23$ ). The ages ranged from 52 to 93. There was a trend toward increasing nerve fiber layer abnormalities with progression and duration of the disease, but it was not statistically significant. However, duration and severity of AD probably affect optic nerve findings. Studies that include only early-onset AD may result in conclusions that the optic nerve is not affected (and therefore no change in the ganglion cells) because the samples studied have not had the progression of the disease to the point at which the ganglion cells have been affected.

### Optic nerve fiber imaging and AD

Parisi et al.<sup>106</sup> used a Stratus-OCT to assess the optic nerve fiber layer thickness in 17 AD individuals and 14 age-matched control individuals and found a significant reduction in nerve fiber thickness in AD individuals compared with normal individuals. The ages ranged from 63 to 77 years and included individuals with only mild AD. In their study of macular volume using a Stratus-OCT, Iseri et al.<sup>70</sup> found that of 28 eyes tested in a group of Alzheimer's participants, there was significant thinning of the macula compared with 30 eyes tested from a group of control participants. Iseri et al.<sup>70</sup> also found that there was thinning of the retinal nerve fiber layer in those with AD compared with age-matched control participants and that both the macular thinning and nerve fiber layer thinning were correlated with the severity of cognitive function loss. These findings were also reported using an OCT by Valenti.<sup>107</sup> Berisha et al.<sup>108</sup> studied a group of glaucoma participants with an average age of 71, AD participants with an average age of 76, and age-matched control participants with an

average age of 72. They found significant differences between the groups in the superior quadrant thickness of the nerve fiber layer when measured with an OCT as well as abnormal cup-to-disc ratios in only the glaucoma group. The glaucoma participants had an average of 106 mm in the superior optic nerve fiber layer, the AD participants had an average of 90 mm, and the control participants an average of 115 mm. This study found that the deficits identified with an OCT are unique to AD and are not an undiagnosed ocular pathology, such as glaucoma. A study undertaken by Paquet et al.<sup>109</sup> looked at not only 15 non-cognitively impaired age-matched participants, 14 participants with mild AD, 12 participants with moderate AD, but also included 23 participants with mild cognitive impairment (considered clinically to be the precursor to AD). They found that the nerve fiber layer was thinned in those with mild cognitive impairment, mild AD, and moderate to severe AD. They also did not find any significant difference between those with mild AD and mild cognitive impairment.

### High temporal frequency visual stimulation and frequency doubling technology and AD

In a study of 10 participants with AD compared with participants with no dementia, Mentis et al.<sup>110</sup> found significant reductions in the response of the magnocellular pathway when measured using positron emission tomography (PET). The stimulus was a grid pattern with increasing temporal frequency. With lower temporal frequencies there were minimal differences, but as the frequencies approached 25 Hz, the reduction in neural response in AD became greater compared with age-matched controls. Another study identified a reduced response in the magnocellular pathway of participants with mild Alzheimer's disease using a high temporal frequency visual stimulation with PET.<sup>111</sup> The visual field test Frequency Doubling Technology (FDT) uses a high frequency target and has identified reductions in those with AD.<sup>6</sup> The FDT is believed to have the capacity to isolate retinal ganglion cells in the magnocellular pathway. The FDT isolates this pathway by utilizing a low spatial frequency sinusoidal grating ( $<1$  cyc/degree) that undergoes a high temporal frequency counter phase flicker at 25 Hz or greater. The subject perceives the targets as small striped square-shaped areas in either central or up to 20° peripheral vision. The threshold strategy of the FDT has been found to be effective even with those with moderate dementias.<sup>6</sup>

### Visual function and AD

Those being treated for AD have been found to have an increased risk of falls.<sup>112,113</sup> Reduced contrast sensitivity, in itself, increases risks for falls.<sup>113,114</sup> There is substantial evidence that contrast sensitivity is reduced early on in AD,<sup>7</sup> and this is further supported by autopsy findings of early pathology in the Brodmann Area 19-visual association

area<sup>5</sup> and findings with Frequency Doubling Technology visual field testing, which uses a low contrast target.<sup>115</sup>

It has been found that up to 30% of elderly over the age of 65 still living in the community experience a fall each year.<sup>116,117</sup> Studies have found that from 10% to 40% of those residing at home are permanently placed in nursing facilities 6 to 12 months after experiencing a hip fracture.<sup>118,119</sup> Those who have multiple falls have impairments in many visual functions that are not considered normal aging, including visual acuity, depth perception, contrast sensitivity, and visual field.<sup>120</sup> There are decreases in contrast sensitivity and losses in visual field with glaucoma, and older individuals who have glaucoma have a higher frequency of injury from falls compared with age-matched controls who do not have glaucoma.<sup>121,122</sup> Furthermore, treatment for glaucoma using beta-blocker eye drops is a risk factor for falls.<sup>122</sup> In a study undertaken by Lord and Menz,<sup>123</sup> it was found that visual input influences posture and sway. Accurate detection of contrast and good stereo function are predictors of sway on a compliant, nonrigid surface and are necessary for stabilization of postural sway.<sup>124</sup> Research into falls has found that ambulation on stairs is a major problem.<sup>125</sup> A study using a Pelli-Robson contrast chart, which measures primarily low spatial frequencies (the spatial frequencies known to be deficit in AD), found significant correlations between deficits of contrast sensitivity and performances on a number of daily living tasks, including walking down steps, reading ingredient labels, writing, reading newspapers, recognizing faces, pouring liquids, and using tools.<sup>126</sup> Those with AD have reductions in contrast sensitivity, placing them at even greater risk for falls and other difficulties in daily living.

Lifestyle, activities of daily living, and decreases in function should be considered for<sup>127</sup>each patient when choosing both medical and optical interventions. Many of the reductions in functional vision impacting those with AD are similar to the visual deficits in the early stages of diseases commonly presenting in a low vision or vision rehabilitation practice such as glaucoma, retinitis pigmentosa, cataract, and early macular degeneration. As with these diseases, as well as the vision concerns of individuals with multi-handicaps brain injury or learning disabilities, optometric practitioners are well trained to handle the complexities of caring for the whole patient, and a thorough comprehensive medical and functional evaluation is key. This is critical for patients with reduced cognition caused by dementia who may have limitations on communication. After careful consideration of risks for falls, an all-inclusive correction minimizing confusion may provide optimum visual function as well as safety. An example of this is multifocal lenses. It has been the practice on the part of several elder care researchers to suggest eliminating multifocal/bifocal corrections with aging, as they increase the risk of falls.<sup>127,128</sup> However, this approach may not be appropriate in some cases of dementia, such as a person with moderate myopia who may have been a lifelong user of bifocal lenses. Exploring the use of high-quality multifocal

progressive lenses with additional treatments to increase contrast and eliminate glare is an option. Suggesting that a person with pronounced dementia as well as moderate myopia not wear multifocals could result in the error of using reading glasses when ambulating or wearing no glasses when ambulating, either of which may present a much greater risk for falls than a high-quality multifocal lens. Other treatments that are common in a rehabilitative practice include glare control, filters to enhance contrast, the use of high-contrast materials, lighting, task-specific glasses, tactile media, environmental modification, enlargement of print, and the use of adaptive tools for daily activities. These are all treatment options that can be considered for the patient with dementia.

## Summary

Optometrists will be increasingly providing care for patients with Alzheimer's disease or families who have a member with Alzheimer's disease. By providing the same high-quality assessment and management both medically and optically as for any other patient, optometrists will be contributing to the overall quality of life for those experiencing cognitive decline. Careful attention to functional difficulties such as contrast difficulties, glare, and visual field deficits will enable a clinician to determine and advise the proper management optically and functionally. The clinician will be able to provide guidance and referral for other needs affected by declines in visual function such as home modification and personal management.

Treatments used for AD also have implications for impact on the visual system. ChEI have been approved for the treatment of AD and are generally the first line of treatment for mild, moderate, and severe AD. The work related to lens opacities and AD have yet to take into account the ChEI and the potential for catarogenic side effects. Cataracts currently are considered a biomarker for AD, and this warrants further investigation.

Glaucoma and AD are both neurodegenerative diseases, and neuroprotective treatments such as memantine are believed to be applicable to both diseases. Immunotherapy for amyloid beta has a positive impact on age-related macular degenerative disease in animal models. It makes sense that if treatment modalities that are applicable to AD, glaucoma, and age-related macular degeneration are similar, then many of the diagnostic and management modalities would also be applicable to both diseases. This appears to be the case. Studies utilizing traditional diagnostic tests for glaucoma, OCT, and preliminary findings with FDT give every indication that the technologies can be practical in the evaluation of AD, even in the early stages when current techniques still have limited ability to differentiate AD from other age-related dementias. Technology and evaluation strategies that have yet to be applied to AD also are promising for monitoring biomarkers of AD and measuring drug efficacy.

There have been substantial gains in health and longevity over the last decades. Along with this, optometrists have been presented with a new set of concerns and issues. As with other serious threats to the visual system and their subsequent effect on quality of life, such as diabetic retinopathy, cataracts, and age-related macular degeneration, optometrists, as a part of a multidisciplinary team, will continue to make strides to help solve the functional problems confronting patients with AD.

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