

# Glaucoma and Alzheimer Disease: Age-Related Neurodegenerative Diseases with Shared Mechanisms?

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## Abstract

Emerging evidence suggests that glaucoma and Alzheimer disease (AD), both age-related neurodegenerative diseases, may share common features and mechanisms. Clinically, support for this association is found in studies showing an increased prevalence of glaucoma among AD patients. However, other studies, including population-based epidemiologic investigations, did not show an increased rate of AD or dementia in patients with glaucoma. Although there is growing interest in a possible relationship between glaucoma and AD, the specific mechanisms that may be common among both diseases are still being examined. It has been demonstrated that optic nerves from AD patients have loss of retinal ganglion cells, as in glaucoma. Furthermore, key processes in AD, including caspase activation, abnormal processing of amyloid precursor protein, and amyloid beta deposition, have been implicated in rodent models of glaucoma. Understanding these pathological processes may shed light on new potential therapies to treat this irreversible and blinding disease.

**Keywords:** Open-Angle glaucoma (OAG); Alzheimer disease (AD); Intraocular pressure (IOP); Neurodegeneration; Epidemiology; Disease mechanisms

Glaucoma is an optic neuropathy that affects an estimated 60 million people and causes bilateral blindness in 8.4 million people worldwide [1]. It is characterized by degeneration and death of retinal ganglion cells and their axons that results in characteristic excavated optic nerve head appearance and corresponding visual field loss. Open angle glaucoma (OAG) is the most common entity and likely consists of a group of disorders. Currently, lowering intraocular pressure (IOP) is the only known treatment to slow glaucoma progression. However, IOP lowering slows but does not cure glaucoma, and many patients continue to decline despite IOP lowering [2,3]. While randomized clinical trials have shown that reducing IOP is effective at delaying the onset and slowing progression [2-8], our understanding of disease pathogenesis is limited. Stressors identified in pressure-induced models of optic nerve damage include neurotrophin withdrawal, excitotoxicity, oxidative stress, and glial activation [9-11].

Among the various neurodegenerative disorders, Alzheimer disease (AD) has been studied most intensively regarding its association with glaucoma. AD is the most common form of dementia that affects an estimated 33.9 million people worldwide and is the sixth leading cause of death in the U.S. [12,13]. Patients affected by the disorder display gradual memory loss and debilitating behavior impairment. Histopathology of AD patients is characterized by amyloid-beta plaques and neurofibrillary tangles of abnormal tau protein deposits in the extracellular spaces of the brain. While there are genetic mutations identified in early-onset AD, the majority of cases are sporadic with an age-related onset that is influenced by multiple genetic and environmental factors.

It has been hypothesized that glaucoma may have common features and shared mechanisms with other neurodegenerative diseases, most notably AD. For example, structural studies of optic nerves from AD patients exhibit retinal ganglion cell loss as is characteristic of glaucoma [14-16]. Furthermore, in human glaucoma specimens, increased levels of abnormal tau protein AT8 was found in the horizontal cells of the retina [17]. Here we review both clinical and laboratory studies that examined the relationship between these two age-related neurodegenerative diseases.

## Clinical Overlap of Alzheimer Disease and Glaucoma

The association between glaucoma and AD was first raised in 1978, when Chandra et al. examined all death certificates in the U.S. [18]. There was a higher frequency of cataract and glaucoma in patients with AD compared to age-, race-, and sex-matched control patients. However, Berkson's bias, wherein patients with chronic illnesses, e.g. AD, require more frequent hospitalization and thus physician examinations, may have resulted in higher rates of diagnosis of cataract and glaucoma [19]. In addition, the study did not identify the nature of the association or whether AD or the ocular diseases occurred sequentially or at the same time or reflected an unidentified set of additional factors.

Several studies have found an increased prevalence of glaucoma among AD patients. In a retrospective chart review of patients with AD, Bayer et al. found that there was an increased occurrence rate of glaucoma (24.5% in AD and 6.5% in the control group) [20]. In a second study, the same investigators performed ophthalmologic examinations including visual fields on nursing home residents with AD in Germany and found an increased prevalence of glaucoma (25.9% in AD individuals compared to 5.2% in those without AD) [21]. While the individuals were matched for age and risk factors of glaucoma, and glaucoma was diagnosed based on characteristic visual field loss and/or glaucomatous optic nerve appearance, only patients with elevated intraocular pressure or suspicious optic nerves underwent visual field testing. Additionally, reliable visual field testing in at least 1 eye was only established in 43 of the 112 persons with AD. In a Japanese population

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with AD, an increased prevalence of glaucoma was documented (23.8% in AD patients versus 9.9% in control patients) [22]. The AD and control persons were also genotyped for the *APOE*  $\epsilon$ 4 allele, which is a major risk factor for late-onset AD. The investigators did not find any statistically significant difference in the percentage of AD individuals with glaucoma who carried the *APOE*  $\epsilon$ 4 allele compared to AD patients without glaucoma. It is also unclear whether visual loss from glaucoma was an independent factor in the institutionalization of the participant, raising the possibility of population bias in the study. Finally, there may be differences by severity of disease, since it is possible that more severe cases of both OAG and AD may be related.

Alternatively, epidemiologic investigations have not found an increased prevalence of AD in glaucoma patients. In one large study using a national registry of hospital admission data in Denmark, patients with a diagnosis of OAG did not have a higher risk of carrying AD diagnosis in the future [23]. The study included more than 11,000 patients with OAG. There were no baseline differences between the patient cohorts, but the study did not match the cohorts on demographics or a comorbidity index. There may also be selection bias for more severe OAG since patients were identified by hospital admission data for surgery. The current largest study on the prevalence of AD in OAG patients used 5% Medicare claim data in the U.S (in press). The study included more than 63,000 patients age 68 and older with an OAG diagnosis from 1991 to 2007 and followed them longitudinally. Patients with a diagnosis of OAG had a lower rate of AD and other dementia diagnosis compared to patients without OAG (6% reduced hazard). The study underwent stringent propensity score matching and was statistically robust under several sensitivity analyses. Both of these investigations did not account for severity of the disease. It is therefore possible that more severe cases of OAG and AD may be related.

Other neurodegenerative disorders have also been linked to glaucoma based on cellular and molecular studies, but limited evidence exists on any clinical relationship. One retrospective chart review of nursing home patients found a higher incidence of OAG in patients with Parkinson's disease compared to the control group (23.7% vs. 7.5% respectively) [20]. However, the study is limited by the small sample size, possible selection bias, and lack of propensity score matching of the control group.

## Disease Mechanisms of Alzheimer Disease and Glaucoma

### Caspases

Apoptosis, or programmed cell death, is a complex system that allows cells to undergo degradation and death when they are no longer needed or functional. It is inappropriately activated in various neurodegenerative diseases. Apoptosis exists in most cells, but the specific molecular pathways may differ. Caspases are a class of aspartate-specific proteases of the interleukin-1 beta-converting enzyme family that play an important role in apoptosis, especially in neuronal death. Caspases have been implicated in the pathogenesis of AD, Parkinson's, and Huntington's disease. Specifically, caspase-3 cleaves amyloid precursor protein (APP) and creates neurotoxic amyloid fragments, which in turn upregulate amyloid-beta (A $\beta$ ) production in hippocampal cells in Alzheimer patients, leading to apoptosis of these cells [24]. Abnormally increased levels of caspase-3-mediated cleavage products of APP and A $\beta$  have been found in retinal ganglion cells (RGC) in rats with ocular hypertension [25-27]. Another caspase, caspase 8, is also activated in RGCs and results in activation of

the apoptotic pathway [25]. These studies point to the fact that caspases play an important role in programmed cell death in both AD and OAG, suggesting the molecular and cellular similarities of glaucoma and other neurodegenerative diseases.

### Amyloid-beta

As discussed above, A $\beta$ , the abnormal cleavage product of APP, is upregulated in the hippocampus of Alzheimer patients and in RGCs in glaucoma rodent models. Moreover, intravitreal injection of A $\beta$  induces RGC apoptosis in a dose dependent manner [28]. Reducing the level of A $\beta$  (either by decreasing A $\beta$  formation with  $\beta$ -secretase inhibitors, increasing A $\beta$  clearance by binding with A $\beta$  antibodies, or inhibiting A $\beta$  aggregation with CongoRed) decreases glaucomatous RGC apoptosis in rats [28]. These findings not only suggest mechanistic links between glaucoma and Alzheimer disease but also provide exciting potential treatment options for glaucoma.

### Synapse loss

In neurodegenerative disorders such as AD, synapse loss precedes neuronal death and may even correlate to early stages of clinical disease [29]. There is mounting evidence that synapses may have independent, degenerative, "synaptoptic" pathways [30,31]. In neurodegenerative diseases, complement activation occurs at the synapses and recruits microglia to phagocytose the complement-bound synaptic components [32]. The complement cascade also can activate the membrane attack complex to initiate synaptic clean-up. Animal studies suggest an important role for glial activation and complement cascade upregulation in initiating synaptic loss in glaucoma [32,33]. However, more data is needed to elucidate the relationship between synaptic loss and the progression or initiation of glaucoma.

### Summary

Neurodegenerative disorders such as Alzheimer disease have intriguing similarities with open-angle glaucoma, both in clinical overlap and mechanistic pathways. As they are both age-related neurodegenerative diseases, future clinical and laboratory studies that focus on shared neurodegenerative disease mechanisms may shine light on new potential therapies to treat this blinding disease.

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