

Senile Dementia and Glaucoma: Evidence for a Common Link

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Abstract

Dementia and glaucoma are both neurodegenerative conditions characterized by neuronal loss leading to cognitive and visual dysfunction, respectively. A variety of evidence exists linking the two diseases including structural signs, specifically degenerative changes within ganglion cells. Both diseases become more prevalent with increased age, but that alone is unlikely to account for the increased co-prevalence of the diseases found in various studies. Neurotoxic substances including abnormal hyperphosphorylated tau and amyloid- β have been found in both disease processes suggesting possible pathophysiologic links between the diseases. The exact mechanism of apoptosis, whether by direct toxicity or potentiation, still needs to be established, but could prove important for both diseases. Another potential link relates to low intracranial pressure in patients with both diseases causing a high translaminal pressure gradient and optic nerve damage in certain patients. While this alone may not account for direct optic nerve damage, it could lead to cerebrospinal fluid (CSF) circulatory failure causing increased neurotoxins along the optic nerves with resultant damage. All of this evidence suggests the need to further study links between the two diseases, as this could prove instrumental in understanding their overlapping pathophysiology and developing directed therapies for both diseases. While this is more thoroughly investigated, it may be prudent to have a lower threshold for a glaucoma work-up in patients with pre-existing dementia.

Keywords: Alzheimer Dementia; Dementia; Glaucoma; Intraocular Pressure; Optic Nerve

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INTRODUCTION

Dementia refers to a group of neurodegenerative conditions in which cognitive and/or behavioral symptoms interfere with an individual's ability to

function, representing a decline from prior levels of functioning.^[1] Alzheimer's disease (AD) is the leading cause of dementia and is present in 60-70% of patients with this age-related process.^[2] The disease is a progressive neurodegenerative disorder characterized by cognitive and behavioral deficits secondary to neuronal cell loss. On the other hand, glaucoma is a progressive optic neuropathy that results in characteristic optic nerve and visual field changes secondary to retinal ganglion cell death. However, given its similarities with AD, it can be thought of as a neurodegenerative disorder as well.

Both neurodegenerative diseases have multiple

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possible overlapping pathophysiologic mechanisms. Intermittent ischemia has been associated with vascular dementia and may cause retinal ganglion cell dysfunction and death. Ischemia can result in oxidative stress leading to the formation of reactive oxygen species and cell damage. Accumulation of neurotoxic factors contributes to cell death in Alzheimer's disease and has been linked to retinal ganglion cell death in glaucoma.

EVIDENCE FOR A DISEASE LINK

Structural Evidence

Hinton et al looked at the postmortem optic nerves of ten patients with Alzheimer's disease and compared them with age-matched controls.^[3] Degenerated axonal profiles, which are characteristic of long-term axonal degeneration, were found at varying levels of severity in AD patients, but were non-existent in the control group. On average, there was a 2-3 times decrease in the number of axons in AD patients. The AD group was also noted to have sparse packing of axons with significant glial replacement compared with tight packing and infrequent glia in controls. AD patients were also noted to have a more homogenous population of remaining axon sizes (1-2 μm) compared with a more varied diameter (0.5-6 μm) in the control population. The authors also examined retinal tissue from four patients with Alzheimer's disease; three of the four eyes demonstrated retinal ganglion cell loss. Even the residual retinal ganglion cells showed degenerative changes, such as cell shrinking or swelling with vacuole formation. There was a corresponding decrease in the nerve fiber layer and two cases demonstrated reactive gliosis. The authors noted that staining for amyloid was negative in the optic nerve and retina sections, as they did not reveal neuritic plaques, neurofibrillary tangles, or amyloid angiopathy.

Blanks et al found the total number of ganglion cell layer (GCL) neurons in the central 3 mm of the retina to be reduced by 25% in AD patients compared with age-matched controls.^[4] They also found that the remaining ganglion cells showed signs of degeneration, such as cell shrinking, vacuole formation and nuclear disintegration. However, these changes did not affect the inner and outer nuclear layers.

Similar degenerative changes were found in a study by Sadun and Bassi^[5] They found the average axon density to be decreased in AD to approximately half that of age-matched controls. Even the remaining axons were noted to have smaller average calibers. Specifically, the magnocellular retinal ganglion cells (RGCs) were selectively affected in early AD. In AD patients, many RGCs showed degenerative changes, including nuclear pyknosis and disintegration, while the nerve fiber layer appeared diminished. The selective damage to RGCs in

AD shows similarities to glaucomatous optic neuropathy where retinal ganglion cell loss is the major pathological feature.^[6]

Similar to the histological studies, clinical assessment of patients with AD has provided support for a link between AD and glaucoma based on structural changes. Using blue-light high resolution photography in 26 AD patients and 30 age- and race-matched controls, Tsai et al found that AD patients had significantly more nerve fiber damage and increased cup-to-disc ratios compared with controls.^[7]

Epidemiologic Evidence

Major epidemiologic studies have demonstrated an increased prevalence of glaucoma with age. In the Beaver Dam Eye Study, investigators found that the prevalence of open-angle glaucoma was under 1% for individuals 46-54 years of age compared to 4.7% in patients ≥ 75 years of age.^[8] In the Baltimore Eye Survey, patients with increased age had increased rates of blindness due to primary open angle glaucoma (POAG) among both whites and blacks.^[9] In the Los Angeles Latino Eye Study, the prevalence of glaucoma was 16-fold higher in Latino patients in the oldest age group (≥ 80 years old) compared with Latino patients from the youngest age group (40-49 years old).^[10] They also found that the oldest group of patients had a 3-fold higher prevalence of ocular hypertension compared with youngest age group. These various studies illustrate the significant role of aging with glaucoma across multiple ethnicities.

The prevalence of dementia also increases substantially with increased age. Based on a systematic review of prevalence studies, the rate of dementia was estimated to be 1.5% in the younger age group (65-69 years old) compared with 24.8% in the older age group (≥ 85 years old) in individuals from Western Europe.^[11]

Various studies have looked into the frequency at which open angle glaucoma (OAG) occurs in AD patients. In a study from Japan, authors compared the prevalence of OAG in AD patients with age-matched controls.^[12] They found that 23.8% of the AD patients had OAG compared with just 9.9% in the control population. Another important finding was that AD patients with OAG had similar intraocular pressures (IOPs) as AD patients without OAG, suggesting that factors other than IOP are leading to glaucomatous damage in AD patients. This finding may also be secondary to the high prevalence of normal tension glaucoma (NTG) in Japanese patients with OAG.

Another study from Germany looked at the prevalence of glaucoma in nursing home patients with AD compared with control patients without AD who were matched for age, gender, family history of glaucoma, myopia, and systemic disease.^[13] The prevalence of glaucoma was significantly higher in the AD group (25.9%) compared

with the control group (5.2%). Although the IOP difference between the AD group with glaucoma and the control group with glaucoma was found to be statistically significant, mean IOP was found to be 18.6 ± 5.9 mmHg and 19.0 ± 3.8 mmHg, respectively. Furthermore, there were no patients with ocular hypertension in the AD group compared with 7.8% in the control group. This led the authors to suggest that the optic nerves of patients with AD may be more susceptible to damage from increased IOP.

In the Three-City-Bordeaux-Alienor study, the authors prospectively looked at a cohort of patients and determined which patients developed dementia during the follow-up period.^[14] Patients were also actively screened to determine the presence of glaucoma. After controlling for confounding variables, the authors found that patients with OAG were four times more likely to develop dementia during follow-up. Specifically, structural markers of optic nerve degeneration, including vertical cup-to-disc ratio ≥ 0.65 and minimum rim-to-disc ratio ≤ 0.1 , were associated with an increased risk of developing dementia. Interestingly, IOP > 21 mmHg and using IOP lowering medications did not demonstrate any association.

However, other studies have not found an increased risk of dementia in patients with glaucoma. Another group used the 5% sample of Medicare claims data to look at patients with OAG and assess if they developed a diagnosis of dementia.^[15] When these patients were compared with a control group without glaucoma, the authors did not find a positive association between glaucoma and dementia. The study had a long follow-up period (14 years), but had some limitations; most notably, diagnoses were based on claims data. Both diseases are difficult to diagnose and the study required that the control group only have one ophthalmologist or optometrist visit in the follow-up period.

In a study from the Danish registry, the authors compared the rate of developing AD in patients with POAG, primary angle closure glaucoma (PACG), cataract, osteoarthritis, and the general population.^[16] They found no increased risk of developing AD in patients within the POAG cohort compared with the other groups. However, one limitation of the study was that identification of patients for different groups was based on discharge diagnoses after hospital admission. This created a bias for patients with more advanced OAG as for a significant time period during the study, patients were hospitalized for glaucoma surgery. Also, the groups used for comparison were not matched based on demographic or comorbidity indices. The study also did not look at if patients within the study had prior diagnoses of glaucoma or AD before being discharged from the hospital.

Neurotoxicity Evidence

A variety of substances have been suggested to be

neurotoxic in both glaucoma and AD. In a study by Yoneda et al, investigators measured β -amyloid₁₋₄₂ (A β 42) and tau levels in the vitreous in patients undergoing vitrectomy for macular hole, diabetic retinopathy, and other ocular diseases with concurrent glaucoma.^[17] Compared with the control macular hole group, there was a significant decrease in the A β 42 level and a significant increase in the tau level in the other two groups. Similar findings have been found in the cerebrospinal fluid (CSF) of AD patients. This suggests the possibility that A β deposition and tau hyperphosphorylation may play a role in retinal degeneration in diseases such as diabetic retinopathy. The patients with glaucoma that were studied had vitrectomy for other concurrent disease including central retinal vein occlusion, age-related macular degeneration, macular hole and others. This makes it difficult to decipher whether the changes were secondary to the glaucoma in these patients or the simultaneous presence of retinal disease. Nevertheless, the study demonstrated significant changes in A β 42 and tau levels within the vitreous in some retinal diseases.

Tau protein, an important microtubule-associated protein, plays a role in axonal transport in healthy nerve cells. Abnormal phosphorylation of the protein can lead to axonal transport problems and neuronal toxicity. Abnormal tau (AT8) has been found in multiple neurodegenerative diseases including Alzheimer's disease. This has prompted groups to assess its role in glaucoma. Gupta et al assessed the presence of abnormal hyperphosphorylated tau protein (AT8) in eyes with advanced glaucoma (requiring enucleation secondary to uncontrolled IOP) and compared them with age-matched controls.^[18] They found that abnormal tau AT8 was detected in the outer border of the inner nuclear layer (INL), localized to horizontal cells in the surgical glaucoma cases, but not in the control cases. They also looked at eyes with incidental OAG, but did not find the abnormal tau protein. The study also looked at localization of normal tau protein, which was found in the inner nuclear retinal layers, including the retinal ganglion cells in the control eyes. However, this was significantly reduced in study eyes with uncontrolled glaucoma necessitating enucleation. The absence of the abnormal tau AT8 in eyes with incidental OAG, but its presence in the uncontrolled glaucoma cases suggests that the abnormal tau AT8 is related to advanced glaucomatous damage.

In a rat model of ocular hypertension, immunocytochemistry showed activated caspase-3 and capase-8 within RGCs, but not in controls.^[19] Furthermore, there was a decrease in full-length amyloid precursor protein (APP) and an increase in amyloid- β containing fragments in the RGCs of ocular hypertensive rat retinas compared with controls. The activated caspases lead to abnormal processing of amyloid precursor protein and amyloid-B formation. The study results concurred

with prior investigations that found that RGCs die by apoptosis.^[20] They suggested two possible pathways through which this may occur: Activation of caspase-8 directly initiating the apoptosis cascade leading to caspase-3 activation and cell death,^[19] or amyloid- β formation, which can cause cytotoxicity and also activate caspase-8^[21] and caspase-3^[22] potentiating apoptosis. Similar pathogenesis has been implicated in AD.^[23,24]

Intracranial Pressure

Another common link found between AD and glaucoma patients relates to intracranial pressure. In a retrospective study of patients who underwent lumbar puncture (LP), CSF pressure was found to be significantly lower in patients with POAG (9.2 mmHg) as compared to patients without glaucoma (13.0 mmHg).^[25] The authors suggested that this pressure difference may lead to a high trans-laminar pressure difference, which subsequently may play a role in glaucomatous optic nerve damage. Trans-laminar pressure difference is calculated by subtracting CSF pressure from IOP and may be an important value with higher values causing more optic nerve damage. The authors also found that the trans-lamina cribrosa pressure difference correlated with the cup-disc ratio.

Berdahl et al also retrospectively studied a larger group of patients who underwent LP and found that patients with POAG had a significantly lower CSF pressure (9.1 mmHg) compared with age-matched controls (11.8 mmHg).^[26] In their study, they also looked at patients with NTG and ocular hypertension (OHT). Patients with NTG had lower average CSF pressure (8.7 mmHg) compared with controls (11.8 mmHg), while patients with OHT had higher average CSF pressure (12.6 mmHg) compared with controls (10.6 mmHg). The authors postulated that the lower intracranial pressure (ICP) in POAG and NTG contributed to the development of glaucoma, while the increased ICP played a protective role in patients with OHT. Limitations in both studies involved their retrospective selection of a small subset of the total number of patients who underwent LP (<0.5% in both).

Given the lack of any prospective evidence, Ren et al created a prospective study to study CSF pressure in patients with OAG, who were divided into two groups (normal IOP group and high IOP group).^[27] The age-matched control group was comprised of patients who underwent LP for other diagnostic reasons. Lumbar CSF pressure was significantly lower in the normal IOP glaucoma group (9.5 mmHg) than in the high IOP glaucoma (11.7 mmHg) or control groups (12.9 mmHg); trans-lamina cribrosa pressure difference was higher in the normal IOP glaucoma group (6.6 mmHg) and the high IOP glaucoma group (12.5 mmHg) as compared with the control group (1.4 mmHg).

CSF pressure has also been reported to be low in some patients with AD. Silverberg et al looked at 181 patients

with AD and no clinical or radiological evidence of normal pressure hydrocephalus (NPH) who had their CSF pressure measured prior to enrollment in a clinical trial for low-flow CSF drainage.^[28] They divided the patients into two subgroups: 7 patients who had a CSF pressure >200 mmH₂O, (mean, 249 mmH₂O; AD-NPH group) and 174 patients with a mean CSF pressure of 103 \pm 47 mmH₂O (AD only group). Based on these results, Wostyn et al hypothesized that there may be a causal relationship between AD and glaucoma secondary to decreased CSF pressure in patients with AD.^[29] They theorized that there may be two subgroups of AD patients which do not have elevated CSF pressure (those with normal CSF pressure and those with low CSF pressure). They believe this supports the idea that low CSF pressure causes an abnormally high trans-laminar pressure difference and possibly subsequent glaucomatous optic nerve damage.

However, the theory of a trans-laminar pressure difference causing backward bowing of the dense connective tissue of the lamina cribrosa and optic nerve cupping has not been supported by the work of Hayreh.^[30] He showed that acutely elevating CSF pressure to 40-60 mmHg in monkeys did not cause any ophthalmoscopically detectable change. Furthermore, enucleated human eyes with acutely elevated IOPs to 50-60 mmHg showed minimal bowing back of the lamina cribrosa.^[31,32]

Circulatory Failure

It has been postulated that while low intracranial pressure may not fully explain the link between AD and glaucoma, its association with circulatory failure may offer an explanation. In another article, Wostyn et al suggest that patients develop low ICP secondary to CSF circulatory failure, causing increased neurotoxins along the optic nerves due to decreased clearance leading to optic nerve damage in NTG.^[33] Support for this theory comes from multiple sources. CSF turnover significantly decreases with age secondary to decreased CSF secretion, increased resistance to CSF drainage, and increased CSF volume in the brain secondary to atrophy.^[34,35] CSF turnover may be important in clearing toxic substances from the CSF.^[36] Furthermore, these aging changes in CSF turnover are increased in AD.^[34-36] Decreased CSF turnover and accumulation of neurotoxins including amyloid- β likely play a role in the pathophysiology of AD. Nucci et al reported a patient with advanced OAG who was started on therapy and had IOPs well controlled after initiation of therapy.^[37] However, after about four years of stability on therapy, the patient had progressive visual loss over seven months. During this time, the patient was noted by his wife to have concomitant onset of memory deficits. Routine lab work, blood pressure monitoring, electrocardiogram, MRI of the brain were unremarkable. The patient underwent an LP to look for markers of

dementia and was noted to have decreased A β 42 and elevated levels of total and phosphorylated tau, consistent with AD. In this patient, the glaucoma progression was associated with CSF alterations suggestive of AD.

Another study by Killer et al theorized that CSF sequestration at the ending of the subarachnoid space around the optic nerve may serve as a sort of a compartment syndrome leading to accumulation of toxins.^[38] They hypothesize that one of the many substances that may be harmful is beta-trace protein, a highly biologically active substance, that could lead to damage to optic nerve axons. This lends to the hypothesis that CSF circulatory failure leads to optic nerve damage.

POTENTIAL THERAPIES

By establishing commonalities in the pathophysiology of the two diseases, new treatment strategies may arise. Guo et al found that amyloid-B localizes to RGCs undergoing apoptosis in an experimental glaucoma model (created by surgically induced chronic OHT), but not in controls.^[39] They also demonstrated decreased RGC apoptosis *in vivo* by targeting various aspects of the amyloid-B (AB) formation and aggregation pathway by using agents to decrease AB formation, clear AB deposition, and inhibit AB aggregation and its neurotoxic effects. Antibodies to AB have been demonstrated clinically to help with clearance of AB plaques and improve cognitive function in some patients.^[40] These findings set up the possibility for future therapy via this neuroprotective approach in both AD and glaucoma.

A review by Chang and Goldberg discusses the potential role of neuroprotection, optic nerve axon regeneration, and neuroenhancement in the treatment of glaucoma, given the limitations associated with IOP lowering therapy only.^[41] Neuroprotective strategies include blocking glutamate excitotoxicity with memantine, an NMDA glutamate receptor antagonist (already approved as a neuroprotective agent in moderate to severe AD), activating alpha-2 receptors via brimonidine, and inhibiting caspase mediated apoptosis. Optic nerve regeneration can be approached by blocking inhibitory signals from glial cells through agents including Rho-kinase inhibitors. This can also be approached by enhancing intrinsic growth ability via agents like neurotrophins. Neuroenhancement may be sought by using agents such as cytidine-5'-diphosphotidylcholine, which is available as an over-the-counter supplement for Alzheimer's disease. In glaucoma patients, this agent has been demonstrated to result in improvement in visual field testing, visual evoked potential, and pattern electro-retinogram (pERG).^[42,43]

In conclusion, physicians including primary practitioners, geriatricians and ophthalmologists should be aware of the shared epidemiology between age-related

dementia and glaucomatous optic neuropathy. Evidence from many studies has shown a link based on structural analysis and potential pathophysiological mechanisms. The American Academy of Ophthalmology Preferred Practice patterns indicate that patients over 65 years of age should be referred for annual eye exams if any risk factor for glaucoma is present.^[44] Given the potential link between the two diseases, ophthalmologists should have lower thresholds for glaucoma work-up in patients presenting with co-existing dementia.

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Conflicts of Interest

There are no conflicts of interest.

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