The ROYAL COLLEGE of
OPHTHALMOLOGISTS

REVIEW ARTICLE

Neurodegeneration in Alzheimer's disease and glaucoma: overlaps and missing links

Sagnik Sen [1] · Rohit Saxena[1] · Manjari Tripathi[2] · Deepti Vibha[2] · Rebika Dhiman [1]

Abstract

The eye is said to be the window into the brain. Alzheimer's disease (AD) and glaucoma both being diseases of the elderly, have several epidemiological and histological overlaps in pathogenesis. Both these diseases are neurodegenerative conditions. Over the years, a consensus has developed that both may be two ends of a singular spectrum of diseases. Epidemiological studies have shown that more Alzheimer's patients may be suffering from glaucoma than general healthy population. Retinal ganglion cell damage is a characteristic of both diseases, along with discovery of amyloid-β and tau protein deposition in the retina and aqueous humor of eye. The latter two proteins are known to be pathognomonic of AD. Other pathways such as the insulin receptor pathway also seem to be affected in both diseases similarly. In spite of these overlaps, there are few missing links which still need more evidence, namely, intraocular pressure mechanisms, cerebrospinal fluid pressure and *trans*-lamina cribrosa pressure gradients, vascular autoregulation factors, etc. Several factors point towards a common pathogenesis at some level for both diseases and prospective studies are necessary to study the natural course of both diseases.

Background

Alzheimer's dementia (AD) is the most common cause of dementia worldwide, which leads to a substantial reduction in activities of daily living among the affected population. AD manifests in the elderly population along with other comorbidities and we are at a very early stage of determining the risk factors associated with it. As age is the most important known risk factor and the average age of the global population is on the rise, it is imperative for us to identify the early changes of Alzheimer's and correlate with the other comorbidities that are present in this age range to establish any missing links in the development of the dreaded condition. Glaucoma is another multifactorial neurodegenerative condition affecting various age groups leading to irreversible loss of vision. Glaucoma for the aged population mainly refers to open angle glaucoma (OAG). Over the years it has been realized that although intraocular pressure (IOP) is the only modifiable and definitely measurable risk factor associated with glaucoma, a background neurodegeneration in the retina and optic nerve is responsible for the visual function loss in these eyes. The pathogenesis of this neurodegeneration has been the topic of recent studies. Present research points to a link between neurodegeneration in the brain and the optic nerve and inner retinal layers, which are an extension of the central nervous system in the form of a peripheral sense organ (the eye). In this review, we have tried to look into the common pathways involved in the pathogenesis and possibilities in management of these diseases that the future may hold for us.

Overlapping features of AD and glaucoma

Epidemiology

Increasing age is a well-known risk factor for AD [1]. Studies have investigated the occurrence of glaucoma especially OAG in AD patients. The Beaver Dam study

✉ Rohit Saxena
    rohitsaxena80@yahoo.com

1   Department of Ophthalmology, Dr. Rajendra Prasad Centre for
    Ophthalmic Sciences, All India Institute of Medical Sciences,
    New Delhi, India

2   Department of Neurology, All India Institute of Medical Sciences,
    New Delhi, India

found that subjects of ages >75 years had a 4.7% prevalence of glaucoma (OAG) as compared with <1% in subjects <55 years [2]. Also, The Baltimore Eye Survey showed that irrespective of race, a higher prevalence of open angle glaucoma was associated with increasing age [3].

Bayer et al. had described the presence of glaucomatous field changes along with cup/disk ratio >0.8 in 29 out of 112 AD patients in a German population [4]. This indicated a prevalence of 25.9% in these patients, as compared with 2.6–4.7% in the general population, as revealed in a number of glaucoma surveys [4]. Moreover, ocular hypertension with normal visual fields and optic nerve heads was also not observed in AD group, as compared with 7.8% in the normal population, thereby suggesting that the optic nerve in AD patients may be less resistant to elevated IOP [4]. Tamura et al. studied 172 AD patients in Japanese population and found that OAG was found in 23.8% of AD patients as compared with 9.9% in healthy controls ($n = 176$) [5]. A retrospective chart review of Canadian AD patients (age > 66 years) found the prevalence of glaucoma as 6.8%, compared with 4.1% in the age-matched control group ($p = 0.02$) [6].

Approaching the idea in the reverse direction, cognitive status assessment has also been performed for elderly patients with glaucoma in some studies. Yochim et al. evaluated a sample of 41 patients of glaucoma (mean age 70 ± 9.2 years, 70% females) with a battery of dementia questionnaires to assess the cognitive status. After controlling for age, 44% of patients showed an obvious cognitive impairment, while 12.2% had a mild cognitive impairment [7]. In contrast to this, Kessing et al. evaluated a Danish population with OAG ($n = 11,721$) and found no association with increased rate of AD development. However, since their study included patients identified by hospital admissions for surgeries, they may have included the most advanced stages of glaucoma leading to selection bias; moreover, a comorbidity matching was also not performed [8].

Recent retrospective studies also have found a positive association between OAG and AD. Lin et al. demonstrated that OAG patients were at a higher risk of AD with an incidence rate of 2.85 per 1000 person-years over a period of 8 years follow-up [9]. In 1351 Taiwanese newly diagnosed AD patients aged >65 years, Lai et al. evaluated the prevalence of glaucoma and compared it against 5329 non-dementia controls, and found an adjusted odds ratio of 1.50 for AD subjects with glaucoma [10]. Compared with retrospective case series, propensity matched longitudinal follow-up studies have come up with more reliable data regarding the association. Ou et al. evaluated OAG patients ($n = 63,325$; both high and normal tension) aged 68+ years and matched control population (by propensity score matching) without having a diagnosis of AD or other

dementia and followed them up for 14 years [11]. They found that there were no statistically significant differences in the percentage of persons in both groups diagnosed with AD or other dementia. Moreover, without controlling for other covariates (retinal degeneration, cataract, gender, race, age, etc), persons with OAG had a reduced rate of AD diagnosis compared with non-OAG controls. However, even this study may have suffered from hidden biases, since AD may have manifested prior to OAG and the available methods of detection might not have picked up the diagnosis of AD or a subclinical cognitive impairment. Moon et al. evaluated 1469 OAG patients and 7345 non-glaucomatous subjects (propensity score matched) over a 10-year follow-up period in Korea. They observed that the OAG group had a significantly higher incidence of AD. Moreover, the risk of developing AD in OAG patients was higher in older age groups (ages > 65 years). However, again the underestimation of the final diagnosis may have been a limitation in this study [12].

OAG includes high-tension glaucoma and normal tension glaucoma (NTG) and currently the consensus regarding absolute distinction between the two patterns of diseases is not well-defined; however, it may be prudent to comment on their association with AD separately. In relation with NTG, however, there are conflicting reports. Bach-Holm et al. identified 69 Danish patients with a diagnosis of NTG with an average follow-up of 12.7 years and found that none of them developed AD [13]. Interestingly, a lot of these NTG patients were using topical alpha-adrenergic agonists (Brimonidine). Based on the recent hypothesis that brimonidine has an additional neuroprotective action in glaucomatous eyes, it has been under investigation for use in AD patients also [14]. However, Bayer et al. have studied NTG in the AD patients and have found a prevalence of 50% NTG in the AD population [4]. Tamura et al. have also found NTG in almost all of their AD subjects [5]. Chen et al. evaluated 15,317 Taiwanese NTG patients (mean age 62.1 ± 12.5 years) and compared them with 61,268 age- and gender-matched controls without glaucoma. NTG patients were seen to have significantly higher cumulative hazard for AD than controls ($p < 0.0001$). Moreover, after adjustment for confounders, NTG group was found to have a significantly higher risk of AD (adjusted hazards ratio 1.52) [15].

Studies on NTG have found a raised level of neurotoxic amyloid-β in the plasma, which is also a typical finding in AD [4]. These studies formed the basis of the possibility of glaucoma being a manifestation of AD in the eye, calling it the ocular AD [16]. Considering this overlap of glaucoma and AD, some trials had been designed with Memantine (NMDA-receptor antagonist) for OAG, a neuroprotective drug used in AD. However, results from studies were inconclusive in this regard [17]. A recent randomized

controlled trial evaluated the effectiveness of oral memantine in OAG population and found that daily memantine treatment did not delay the progression of glaucomatous damage [18]. Recently, clinical trials are being designed to focus on developing neuroprotective treatments for NTG patients and have not included the glaucoma patients with high IOP [13]. Chen et al. found that the glaucoma eye drops used in their NTG patients were neither significant risk factors nor protective factors for development of AD [15].

Genetic overlaps

Several studies have observed genetic overlaps between AD and glaucoma. The genotype of the Apolipoprotein E (*APOE*) gene has been studied most commonly in this regard, since it is one of the major risk factors for AD. APOE is important in lipid metabolism and transport of cholesterol and triglyceride [19–22].

In the retina, ApoE protein is synthesized by Müller cells, absorbed by RGCs and transported to the optic nerve and this is a cycle of metabolism and neuronal survival for the RGCs. ApoE is also involved in other cellular functions, such as tissue repair, cell growth and differentiation, and immune mechanisms [23]. Copin et al. found that polymorphism of *APOE* promoter gene may affect visual field loss and optic nerve damage in POAG patients [24].

There was no proper consensus about the exact association between *APOE* gene and POAG, even after multiple studies had been done. A recent metanalysis included 12 such studies on *APOE* gene and POAG. The authors found significant association between *APOE* gene and POAG in the genetic models of *ε4/ε4* versus *ε3/ε3* and concluded that *ε4/ε4* genotype is associated with increased risk of OAG among Asians [25]. Moreover, this risk was not different between high-pressure glaucoma and NTG populations [25]. Individuals with *APOE ε4* have been seen to have severe amyloid plaques, neurofibrillary tangles, and more mitochondrial damage than patients with other polymorphisms [26]. Similarly, *APOE* polymorphisms in OAG may lead to increased degeneration of RGCs and axons.

In contrast to the above findings, Tamura et al. had reported the prevalence of *APOE ε4* in AD patients with and without OAG, and found no significant difference, thereby suggesting that other genetic factors apart from *APOE* may be responsible for their association.

Pathological changes

Retinal ganglion cells and nerve fiber layer

Histopathological changes of an Alzheimer's brain, namely neuronal apoptosis, amyloid-β plaques, neurofibrillary

tangles, and vacuolar degeneration have also been observed within the retina [27–29]. On autopsy analysis of specimens of retina from AD patients, apart from an extensive optic nerve axonal degeneration, a reduction in the number of retinal ganglion cells (RGCs) in the ganglion cell layer (GCL) has also been observed [29, 30]. Nerve fiber layer thinning has been hypothesized to occur due to a degeneration of the RGC axons, which may precede the cognitive impairment in AD [31, 32]. Histologically observed loss of large M cells of the GCL has been postulated to be responsible for contrast sensitivity dysfunction in AD [31–33]. This progressive death of neurons and accumulation of neurofibrillary tangles (tau protein) and amyloid-β plaques may also damage the lateral geniculate body neurons connected to the damaged RGCs and affect various layers and cell types within the cortex, destroying the cortical pathways of higher learning and leading to cortico-cortical disconnection [34]. It has been proposed that GCL thinning may be an important prognostic indicator for AD patients [35].

Optical coherence tomography (OCT) has become a very useful noninvasive tool for diagnosis of macular diseases and optic disc changes, with various currently available algorithms to separately analyze the individual layers of the retina [36]. Retinal nerve fiber layer thinning has been noted in a number of studies conducted in AD patients using OCT [37]. This degeneration of nerve fiber layer in AD patients has been seen to occur in all quadrants of the optic disc, with a preference towards the superior and inferior quadrants, the reason for which is unknown [38, 39]. This nerve fiber layer thinning has been believed to be secondary to damage to ganglion cell bodies [31, 32].

OCT studies in glaucoma have found a preferential thinning of nerve fiber layer in the superior and inferior quadrants, similar to that seen in AD [40]. RGCs are the end point of damage in glaucoma patients as well [41]. Glaucomatous changes manifest as nerve fiber layer thinning and glial cell activation secondary to RGC apoptosis, which has also been observed in AD [38, 42–45]. The loss of the RGCs, their axons and the final loss of supporting glial cells leads to the excavation of the optic nerve head characteristic of glaucoma [46]. The damage to RGCs occurs by means of various combinations of apoptosis, oxidative stress, mitochondrial dysfunction, excitotoxicity, and insulin resistance [47–49].

Amyloid precursor protein and beta-amyloid

RGC and retinal pigment epithelial cells are responsible for amyloid precursor protein (APP) synthesis and secretion in the posterior segment of the eye [50]. Healthy individuals process APP with alpha-esterase into alpha-amyloid. However, in diseased individuals, APP is converted into

beta-amyloid by beta-esterase. Beta-amyloid may reach toxic levels with a high penetrance, aggressively targeting neurons [51, 52]. Caspases 3 and 9 have been linked to APP misprocessing which eventually leads to cellular death [53–55]. The amyloid metabolism may be guided by caspase-activation in both glaucoma and AD.

Few studies have reported a deposition of amyloid-β peptides in the RGC layer in AD with a possible immunological pathway of RGC destruction, which is reflected as a loss of scotopic threshold response [56–58]. Guo et al. demonstrated in mouse models of AD that amyloid-β levels were upregulated in RGCs of rodent retina and RGC apoptosis could be induced by injecting intravitreal amyloid-β [59]. Interestingly, hyperspectral imaging of retina strongly suggests that this early amyloid-β beta related retinal dysfunction may begin during the asymptomatic stage [60]. Recently, hyperspectral imaging was performed in patients with confirmed amyloid-β deposition in brain detected using positron emission tomography (PET), and the model developed by the authors could accurately predict brain Aβ PET status in a validation cohort of AD patients and also, in a cohort of mice model of AD [61].

Beta-amyloid deposited in extracellular spaces eventually start an inflammatory cascade by triggering TNF-alpha, cytokines, etc leading to pathological changes characteristic of AD. Neuroinflammation is also believed to be the causative factor behind the development of glaucoma and Parkinson's disease [62]. Szekely et al. however found inconclusive evidence of beneficial effects of anti-inflammatory therapy (nonsteroidal) on neuroprotection [63].

Janciauskiene et al. have uniquely demonstrated the presence of amyloid-β peptides (A-β1-38, A-β1-40, and A-β1-42) in aqueous humor of glaucoma patients (pseudoexfoliation), strengthening the concept of a link between age-related eye diseases and AD [64, 65]. Guo et al. have demonstrated, using experimental glaucoma models, that amyloid-β colocalizes with RGCs inducing significant apoptosis in vivo in a dose- and time-dependent manner. They have further demonstrated that targeting and inhibiting different components of amyloid-β formation and aggregation pathways may be effective therapeutic strategies in glaucoma management [59].

Mitochondrial dysfunction may occur because of amyloid-β induced opening of mitochondrial pores, which may play a role in apoptosis. Moreover, Osborne et al. have observed that the mitochondria in glaucomatous RGCs are in a low energy state because of reduced vascular perfusion and are incapable of getting rid of excess reactive oxygen free radicles [66–69]. In this regard, antioxidant molecules such as Vitamins C and E and Gingko biloba have been studied for their neuroprotective effect in glaucoma [51, 70, 71].

Tau protein

Tau protein also has been postulated as a common pathogenetic factor, with its presence in cerebrospinal fluid (CSF) of AD patients and in the horizontal cells of retina, optic nerve, and peripapillary region in glaucoma patients [72–75]. In mouse models of Alzheimer's disease, investigators have found early accumulation of tau proteins in the retina prior to beginning of cognitive defects [76]. Tau accumulation has also been observed in the cell body and dendrites of RGCs in glaucoma, leading to neuronal death [77]. Tau protein is believed to affect the overall retinal function by causing dysfunction in axonal transport and functionality [77]. The decrease of tau burden in the retina appears to have a widespread beneficial effect on the overall health of RGCs leading to improvements in axonal transport and functionality.

Till date it is unclear whether in glaucoma, axons are damaged before the ganglion cells and whether glial cells are affected before or after RGC loss as a reactionary mechanism [78]. However, in mouse models of AD, it has been observed that RGC cell bodies get affected prior to the dendrites, which also precedes the loss of dendrites in hippocampal pyramidal neurons with frank pathological changes of AD [79].

Insulin receptors and neurodegeneration

Insulin receptors (IRs) have been found to be necessary for the physiological functioning of the visual system, including the RGCs [80]. IR is a transmembrane receptor activated by insulin and is expressed in the central nervous system. Although their exact function in CNS has not been studied in detail, they are believed to be involved in neuronal functions and control many cellular processes, such as cell growth and differentiation [81]. Reduced IR expression has been seen in AD and Parkinson's disease [82, 83]. IRs may prevent the formation and increase the degradation of AD amyloid plaques, and inhibit the neurofibrillary tangle formation [84, 85]. Human RGCs have shown expression of insulin and insulin-like growth factor (IGF-1) immunohistochemically, and may be mediators of RGC survival [86, 87]. One study found that the neurodegeneration typical of AD includes aberrations in expressions of insulin and associated genes, with more significant affection in advanced cases [82, 88]. It has been hypothesized that insulin and IGF-1 pathways control neuronal viability, tau protein expression and mitochondrial function. Insulin resistance has been reported to be associated with a rise in IOP and insulin induced hypoglycaemia lowers IOP acutely [89, 90].

Malfunctioning of IRs thus play a role in neurodegeneration and may be a common risk factor responsible for

AD and glaucoma. Further studies are needed to elucidate this mechanism.

Missing links

Intraocular pressure

Although IOP is a modifiable risk factor for glaucomatous damage, previous damage to optic nerve head due to chronic raised IOP is mostly irreversible. It has been noted that an abnormally high trans-lamina cribrosa pressure difference, due to high IOP or low cerebrospinal fluid pressure (CSFP), may result in glaucomatous optic nerve damage [91]. Moreover, rather than steady stress, repeated mechanical stress due to fluctuating IOP may be more harmful to the optic nerve head neurons with faster progression of visual field damage [92–95].

Cerebrospinal fluid (CSF) pressure

In a study measuring CSF pressure in glaucoma patients, it was found that CSF pressure was lowest in NTG patients, higher in HTG patients and highest in normal controls [96]. Also, the *trans*-lamina cribrosa pressure difference was highest in the HTG patients, followed in order by NTG patients and normal controls. In cases of normal-pressure hydrocephalus patients, *trans*-lamina cribrosa pressure has been seen to fluctuate, due to CSFP fluctuations and ICP is not steadily normal, unlike what the name of the disease suggests [97–99]. This leads to shear stress on the lamina leading to RGC degeneration. Silverberg et al. studied patients with AD and found a gross overlap between AD and normal-pressure hydrocephalus, and hypothesized that these diseases may represent two ends of CSF circulatory failure [100]. Moreover, Wostyn et al. also hypothesized that the patient groups having low to normal CSF pressure may have a causal association with glaucoma [101].

CSF changes

CSF turnover has been seen to slow down with age, secondary to reduced secretion and resistance to drainage, causing accumulation of neurotoxins along optic nerve. These ageing changes in CSF are seen in AD patients. Moreover, a new concept of CSF sequestration has been proposed by Killer et al. which states that CSF may collect around the optic nerve at the ending of the subarachnoid space leading to a compartment syndrome associated with accumulation of toxins [102]. The accumulated toxins include amyloid-β proteins, which are integral to the pathophysiology of AD.

Vascular flow regulation

Apart from elevated IOP, certain vascular dysregulation factors may contribute to the initial glaucomatous insult to the optic nerve, in the form of changes in axoplasmic flow and microcirculation at the lamina cribrosa, with additional changes in laminar connective tissues [103]. Moreover, this also leads to reduction of factors, such as brain-derived neurotrophic factor, with release of neurotoxic factors within the retina, namely glutamate, nitric oxide and free radicals. Moreover, retinal hemodynamic changes in AD patients are similar to glaucoma patients who also demonstrate narrowing of vessels with reduced flow [104]. This vascular theory suggests that glaucomatous optic neuropathy results from inadequate blood supply to the optic nerve head due to either increased IOP or risk factors causing reduced ocular blood flow [105]. The reduction in blood flow in glaucoma occurs in both early and late stages [106, 107]. These vascular disturbances are more pronounced in normal-tension glaucoma [108–110]. Recently, damage in glaucoma has been realized as more of a reperfusion injury rather than an ischemic change [111, 112]. Postischemic injury brains have been found to contain APP plaques and phosphorylated tau protein in different parts and this has suggested an association between brain ischemia and AD [113–115]. General consensus has been formed that amyloid plaques and neurofibrillary tangles are products of neuronal ischemic injury [116, 117].

Conclusion

To summarize, AD and glaucoma share multiple common biochemical and pathological changes. Both AD and glaucoma are slowly progressing age-related neurodegenerative disorders and may after all be manifestations of the same pathogenetic process with heterogenous presentations. We have collated certain overlapping epidemiological and pathologic changes that link the two diseases. But some missing links need to be further explored to better understand the relation between the two pathologies. Long-term prospective cohort studies are required to determine natural history of AD and its relation to glaucoma and related disorders.

Compliance with ethical standards

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