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REVIEW ARTICLE

Glaucoma and Alzheimer Disease: One Age-Related Neurodegenerative Disease of the Brain

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Abstract: ***Background*:** Open Angle Glaucoma (POAG) is the leading causes of irreversible blindness worldwide. Elevated intraocular pressure is considered an important risk factor for glaucoma; however, a subset of patients experiences a progression of the disease even in presence of normal intraocular pressure values. This implies that risk factors other than intraocular pressure are involved in the pathogenesis of glaucoma. A possible relationship between glaucoma and neurodegenerative diseases such as Alzheimer Disease has been suggested. In this regard, we recently described a high prevalence of alterations typical of glaucoma, using Heidelberg Retinal Tomograph-3, in a group of patients with Alzheimer Disease. Interestingly, these alterations were not associated with elevated intraocular pressure or abnormal Central Corneal Thickness values. Alzheimer Disease is the most common form of dementia with progressive deterioration of memory and cognition. Complaints related to vision are common among Alzheimer Disease patients.

***Methods*:** In this paper researches related to glaucoma and Alzheimer disease are reviewed.

***Results*:** Diseases characteristics, *i.e*. common features, risk factors and pathophysiological mechanisms gathered in the recent literature do suggest that Alzheimer Disease and glaucoma can be considered both age-related neurodegenerative diseases that may co-exist in the elderly.

***Conclusion*:** In conclusion, preclinical and clinical evidence gathered so far support the notion that glaucoma is a widespread neurodegenerative condition whose common pathogenetic mechanisms with other diseases, *i.e.* Alzheimer Disease, should be further investigated as they may shed new light on these diseases improving both diagnosis and treatments.

Keywords: Alzheimer's disease, glaucoma, neurodegeneration, age-related diseases, optic nerve, magnetic resonance imaging, heidelberg retinal tomography, optic coherence tomography.

1. INTRODUCTION

Glaucoma, with more than 60 million people affected in the world, is the leading cause of irreversible blindness [1, 2]. This optic neuropathy is characterized by progressive optic nerve head (ONH) cupping, retinal ganglion cells (RGCs) death and thinning of the nerve fiber layer (NFL). The pathogenesis of the disease is still poorly understood, but age [3, 4] and elevated intraocular pressure (IOP) [5] are considered important risk factors. However, a subset of patients experiences a progression of the disease even in the presence of normal or medically controlled IOP values. This implies that risk factors other than IOP may be involved in the pathogenesis of glaucoma [6]. In this regard, several studies report data documenting the association between glaucoma and other diseases [7, 8]. Primary open-angle glaucoma (POAG) has been associated with modifications of the cardiovascular system, immune system, autonomic nervous system, retinal blood flow as well as endocrine, psychological, and sleep disorders. An association between POAG and neurodegenerative diseases of the central nervous system, such as Alzheimer's disease and Parkinson's disease, has also been reported. The latter association is also supported by studies with magnetic resonance showing transsynaptic degeneration affecting the central areas of the visual system in patients with glaucoma [9, 10]. This shed new light on the disease giving life to the new theory suggesting that the disease could be considered not only an ocular disease but a more complex neurodegenerative process that affect the entire visual system [11-15]. Accordingly, a relationship between glaucoma and neurodegenerative disease such as Alzheimer's Disease (AD) has been suggested [16-18].

AD is the most common form of dementia with progressive deterioration of memory and cognition. It is characterized by the loss of neurons in the hippocampus and cerebral cortex caused by plaque accumulation of abnormally folded amyloid beta (Aβ) and tau protein in the brain. Complaints

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related to cognitive visual changes are common among AD patients. In particular, difficulties in reading and finding objects, altered depth and color perception, impaired spatial contrast sensitivity or difficulties in perceiving structure from motion have been reported [20]. This visual alteration can be related to any dysfunction occurring in the visual pathway, including damages in the visual cortical and pre-cortical areas [19, 20].

In this paper, we will discuss the common features, risk factors and pathophysiological mechanisms which suggest that AD and glaucoma can be considered both age-related neurodegenerative diseases that may co-exist in the elderly.

2. EXPERIMENTAL EVIDENCE FROM ANIMAL MODELS

The hallmark of AD is the neurotoxic Aβ deposition and plaque formation in the brain that is considered the major cause of cellular metabolism disruption with consequent neuronal cell death [21, 22]. Recent studies reported that functional modifications induced by injury of synapses [23] precede the degeneration of RGCs. Jakobs *et al*. stated that, in glaucoma, remodeling of retinal circuitry, RGC dendritic arbor and axonal atrophy come first to the death of the RGCs [24]. This suggests that synapses impairment is followed by consequences for RGC viability. Greater retinal levels of soluble Aβ in AD may alter synaptic circuitry and retrograde transport of neurotrophic factors in the optic nerve axons causing RGCs death [25, 26].

Several papers on animal models focused on the relationship between Aβ and glaucoma. Studies on rat models reported that RGCs constitutively express Aβ-42 [27]. Cryosections or flat-mounted retinas of rat eyes were used for testing Aβ-42 by immunocytochemistry staining. Aβ-42 expression started 15 days after birth and increased with aging of the rat, reaching the highest level in 60 days after birth. Additionally, the expression of Aβ-42 was not detected in rats kept under dark, demonstrating that light is essential for the expression of Aβ-42 in retina. Guo *et al*. carried out four groups of experiments to explore the potential role of Aβ in glaucoma [28]. In the first experiment, the histological analysis of eyes with induced ocular hypertension revealed a significant increase of Aβ-42 in the apoptotic RGCs in an established rat model of glaucoma. Then the Authors assessed Aβ neurotoxicity on RGC cells *in vivo*, clearly demonstrating that Aβ colocalizes to apoptosing RGCs suggesting the potential involvement of Aβ neurotoxicity in the development of glaucomatous RGC death. Interestingly, the intravitreal injection of Aβ-42 resulted in a time and dose dependent RGC death, confirming a role of Aβ-42 both in glaucoma and in AD. Finally, they studied the efficacy of targeting Aβ using single- and combined-agent therapies in reducing RGC apoptosis. For this purpose, several different methods were used to reduce the effectiveness of Aβ in this model, including a β-secretase inhibitor (βSI), Congo Red (CR) and Aβab. Overall, Aβab was the most effective in preventing of RGC apoptosis. However, the study also suggested that the combination of the different agents altering the Aβ pathway at several levels may be the most effective therapeutic strategy [28].

Immunostaining studies by Kipfer-Kauer *et al*. [29] confirmed the results of previous researches [30, 31] reporting caspase activation and abnormal processing of amyloid precursor protein (APP) in RGCs of rats with induced chronic ocular hypertension. The Authors described elevated Aβ and APP levels in ocular hypertensive retinas, especially in the optic nerve, the RGC layer, and the pial/dural complex [29]. This could be the consequence of abnormal APP-splicing induced by elevated IOP. In keeping with this hypothesis, Gupta *et al*. reported increased Aβ deposition in the retinas of an APP-PS1ΔE9 mouse model of AD showing consequent loss of inner retinal functions [32]. Perez *et al*. have also confirmed this in a study on APPswe/PS1ΔE9 transgenic mice showing that Aβ deposition disrupts retinal structure possibly leading to the visual deficits [33]. Incidentally, behavioral studies on transgenic mice by Arendash *et al*. confirmed the presence of visual alterations in these animals suggesting a connection between overexpression of APP, production and deposition of soluble Aβ and induction of hyperphosphorylation of Tau [34]. The formation of Tau inclusions is considered another hallmark of AD and altered Tau levels have been also detected in retina and optic nerve of patients with glaucoma [35]. In this regard, Gasparini *et al*. histochemically confirmed that hyperphosphorylated Tau accumulates in RGCs and in cultured retinal explants of human P301S tau transgenic mice suggesting a role of this protein in the induction of visual dysfunctions. In particular, hyperphosphorylated transgenic tau accumulates in the nerve fibre layer and aggregates into filamentous inclusions in RGCs of human P301S tau transgenic mice [35].

Chiasseu *et al*. reported that endogenous retinal tau is increased by ocular hypertension [36]. Mislocalization of tau in the somatodendritic compartment and depletion from the axons of the RGCs has been reported in the eyes of animals with ocular hypertension. Interestingly, intraocular administration of short interfering RNA against tau promoted RGCs survival suggesting a role of tau in RGC neurodegeneration in glaucoma.

3. EPIDEMIOLOGICAL AND EXPERIMENTAL EVIDENCE IN HUMANS

Several epidemiological studies focused on the potential association between AD and glaucoma with contrasting results. The first report dates 1986 when Chandra and colleagues analyzed all death certificates in the United States for 1978 on which diagnosis of senile and pre-senile dementia was mentioned showing an increased prevalence of glaucoma among those subjects [37]. These results were subsequently confirmed by 2 observational case series that respectively included a chart of 49 and 112 patients with AD from different nursing homes in Upper Bavaria, Germany. The first study revealed a 24,5% prevalence of glaucoma in AD subjects compared to the 6,5% of the control group [38], while the second study reported a 25,9% prevalence of glaucoma with respect of 5,2% of non-AD individuals [39]. Similarly, Tamura *et al*. reported a 23.8% prevalence of glaucoma in a chart of 172 AD patients institutionalized in four Japanese Hospitals compared to the 9.9% of the control group. Interestingly, no difference between open angle glaucoma (OAG) and non OAG was found [40]. Moreover, studying the same topic from the opposite point of view, Lin *et al*., in a retrospective study on patients with and without POAG aged 60 years and older, reached the conclusion that

POAG patients had a higher risk of developing AD than controls [41]. In a recent study, our group examined AD patients using Heidelberg Retinal Tomograph III (HRT-III) and Frequency Doubling Technology (FDT) perimetry showing a higher prevalence of glaucoma-like alterations in the AD group when compared to controls (27.5 *vs*. 7.5%; p=0.003; OR=4.69). It is interesting that AD group had higher glaucoma-like alterations even in presence of normal, or even lower, IOP values than the control group [13]. A similar study by Kurna *et al*. reached contrasting results showing no statistically difference between AD and controls regarding the tested morphological parameters, *i.e*. the optic disc [42].

Similarly, several studies did not support the association between POAG and AD. Kessing *et al*. investigated whether POAG was associated with increased risk of developing AD in a nationwide case register linkage study. A total of 11,721 POAG patients were included in the study, however an increased rate of subsequent AD was not found compared to patient affected by primary angle closure glaucoma, cataract, osteoarthritis or general population [43]. Bach-Holm *et al*. found similar results in a nationwide health care register study that included 69 patients with normal tension glaucoma (NTG). In this study, NTG was not associated with AD as none of the patients included developed the disease. However, the Authors stated that the lack of association could be related to the wide confidence limits led by the small number of subjects included in the study [44]. In addition, other studies reported that the coexistence at the individual level of AD and POAG is not different from that expected by chance [45]. Furthermore, a longitudinal retrospective cohort study concluded that individuals diagnosed with OAG had a decreased rate of AD compared to subjects without OAG [46].

4. COMMON PATHOGENIC MECHANISMS

On these bases, similar degenerative processes could affect both the eye and the brain [15, 20]. Several studies attempted to support the association between AD and glaucoma trying to find a link in the pathogenic mechanisms of the two diseases.

Post-mortem examination of optic nerves of patients with glaucoma showed a degeneration of the axonal profile like the long-term axonal degeneration that can be found in AD patients at different stage of the disease. Overall, the number of axons was 2-3 times reduced in AD patients and it was replaced by glia tissue. Similar results appeared in retinal tissue specimens from four patients with AD that showed both RGCs loss and shrinking and swelling of the residual RGCs [47]. Similar signs of degeneration in RGCs and a 25% loss of neurons in the ganglion cell layer (GCL) were reported by Blanks *et al*. in AD patients compared with age-matched controls [48]. Signs of RGCs degeneration and half of the average axon density were also confirmed in a subsequent study by Sadun and Bassi [49].

Varieties of substances have been suggested to be neurotoxic in both glaucoma and AD. The attention has been recently focused in the altered levels of Aβ and tau proteins found in AD as well as in glaucoma. In particular, a study on collected vitreous samples from patients who underwent vitrectomy found a significant decrease in the Aβ-42 level and a significant increase in the tau level in patients with glaucoma compared to controls [50]. Gupta *et al*., in a study on 11 surgical eye specimens confirmed the presence in the posterior retina of abnormal hyperphosphorylated tau AT8, a marker of injury in AD and other neurological diseases, and of decreased concentration of normal tau-protein (BT2) [22]. In another paper, Inoue and collaborators analyzed aqueous humor sample collected from 38 patients with cataract, 32 patients with exfoliation glaucoma and 20 patients with POAG [51]. They measured aqueous levels of apolipoprotein (Apo) A1, ApoCIII, ApoE, transthyretin (TTR), complement factor H, complement C3, and α2-macroglobulin (α2M) showing higher levels of Apo A1, ApoCIII, ApoE, TTR and α2M in POAG and pseudoexfoliative in glaucoma patients then in subjects with cataract. Moreover, mean deviation values from visual field (VF) tests positively correlated with Apo A1, ApoE, TTR complement factor H in open-angle glaucoma patients.

In this regard, our group described the case of 69-year-old man who was diagnosed an advanced open-angle glaucoma in 2005 [52]. IOP was medically controlled but, four year later after the diagnosis, the patient experienced an important worsening of the VF although IOP was still in the normal range. Concomitantly, the patient showed initial signs of cognitive impairment, therefore after routine lab works, blood pressure monitoring, electrocardiogram and MRI that resulted unremarkable, neurological screening and cerebrospinal fluid markers were assessed. Interestingly, the patient showed decreased Aβ-42 (226 pg/mL) and elevated levels of total and phosphorylated tau (t-tau and p-tau) (655 and 105 pg/mL, respectively) consistent with the diagnosis of AD. This in also in line with the results of a cross-sectional study by Sunderland *et al*. in which baseline CSF Aβ-42 and tau levels in AD patients and controls were compared [53]. Meta-analysis involved 17 studies of CSF Aβ and 34 studies of CSF tau.

In this review, altered cerebrospinal fluid (CSF) circulatory dynamics failure has been suggested as a potential explanation of the pathogenesis of AD and glaucoma [54]. This is a common process that appears with ageing. In particular, it is possible to observe a decrease of CSF secretion, an increased resistance to CSF drainage, and an increased CSF volume in the brain consequent to atrophy [55-57]. Wostin and colleagues suggested that CSF circulatory failure induces a secondary lowering of intra cranial pressure (ICP) which results in a reduced clearance of neurotoxin, such as Aβ and tau, along the optic nerve causing oxidative stress and degeneration of RGCs in NTG [58]. This is also in line with the compartment syndrome theory postulated by Killer *et al*. [54]. They suggested that the subarachnoid space (SAS) of the optic nerve resembles a *cul de sac* which has the potential to decrease CSF turnover and that compartmentalization would lead to inflammatory changes and mechanical stress on the arachnoid as well as on glial cells in the optic nerve, leading to an increased expression of neuroinflammatory molecules.

Another possible common link found between glaucoma and AD is the presence of an altered ICP. To support the notion that CSF pressure may play a causative role in the pathogenesis of POAG, Berdahl *et al*. compared CSF pressure of patients with POAG with that of non-glaucomatous

patients. In this retrospective study, CSF pressure values of 28 patients who had POAG and 49 patients who did not have POAG were analyzed [59]. Interestingly, CSF pressure was significantly lower in POAG patients compared with that in nonglaucomatous controls supporting the notion that CSF pressure may play an important contributory role in the pathogenesis of POAG. In another study, Berdahl *et al*. compared ICP in subjects with POAG, NTG, and ocular hypertension (OHT) with that in subjects disease-free reporting that ICP was lower in POAG and NTG but elevated in OHT [60]. Thus, ICP may play a role in the development of POAG and NTG and in preventing the progression of OHT to POAG.

Given the limitation of these retrospective studies, and the lack of any prospective report, Ren *et al*. created a prospective interventional study that included 43 patients with OAG (14 with normal IOP, and 29 with high IOP) and 71 subjects without glaucoma to evaluate whether a low CSF pressure was associated with OAG in the eyes with normal intraocular pressure [61]. In OAG group with normal IOP, CSF pressure resulted abnormally low, leading to an abnormally high trans-lamina cribrosa pressure difference. In particular, CSF pressure was lower in the OAG group with normal IOP (9.5+/-2.2 mmHg), than in the high IOP OAG group (11.7+/-2.7 mmHg) or the control group (12.9+/-1.9 mmHg). It is conceivable that a low CSF pressure in the normal IOP group may have the same consequence of high IOP than that with the high IOP [62, 63]. Accordingly, the glaucomatous VF defect positively correlated with the trans-lamina cribrosa pressure difference and inversely correlated with the CSF pressure.

Incidentally, there are reports showing that some patients with AD present with low CSF pressure [64]. 222 AD subjects were screened by history, neurological examination, and radiographic imaging to exclude those with clinical or radiographic signs of normal pressure hydrocephalus (NPH), and 181 of those had CSF pressure measurements recorded. Interestingly, a substantial proportion of AD patients had very low CSFP and only 4% of the included subjects had elevated CSF pressure. Given this observation, and given that low CSF pressure may create an abnormal high trans-lamina cribrosa pressure difference leading to glaucomatous damage [59, 65], Wostyn *et al*. suggested that this pressure gradient may explain greater risk of developing glaucoma in AD subjects [66].

However, several studies did not support this theory and Wostyn himself suggested that a low ICP could not completely explain alone the link between glaucoma and AD [67-69]. Thus, he suggested that the combination of low ICP and CSF circulatory failure might offer a more suitable explanation [57]. Moreover, recently Wostyn *et al*. also proposed a new theory based on the failure of the glymphatic system [69]. This is a recently defined system of perivascular channels, formed by astroglial cells, along which a large amount of subarachnoid CSF recirculates through the brain parenchyma, helping the clearance of interstitial solute, as well as Aβ, from the brain. Beside waste elimination, this system may contribute in distributing essential compounds such as lipids, glucose, amino acids, and neurotransmitters in the brain [70]. It is intriguing that glymphatic system function sharply decreases during aging [71]. It has been suggested that a failure of the glymphatic system may contribute in a deficient clearance of Aβ in neurodegenerative diseases such as AD and, possibly, in glaucoma. This is suggested by recent literature reporting the presence of a similar system in the retina that may be involved in ocular diseases such as age-related macular degeneration, retinal vasculitis [72], and glaucoma as well [73]. Interestingly, a postmortem study confirmed the accumulation of India ink in paravascular spaces around the central retinal artery and vein after bolus injection into the subarachnoid space of the optic nerve [74]. In addition, evidence for a glymphatic system in human, primate, rat, and mouse retina has been reported [74]. In this regard, Sakamoto *et al*. speculated that paravascular space surrounds the branches of the central retinal vessels serving as drainage channels from the subarachnoid space around the optic nerve [75]. Therefore, high IOP, decreased ICP or decreased lamina cribrosa thickness may increase the pressure barrier against which paravascular flow needs to occur altering glymphatic fluid transportation and causing a reduction of Aβ clearance and subsequent glaucomatous optic neuropathy [74].

Kountouras *et al*. have proposed an infective hypothesis [76]. The Authors suggested a potential association between *Helicobacter pylori* (Hp) infection and glaucoma. This hypothesis is subsequent to the documentation of a beneficial effect of Hp eradication upon AD and glaucoma progression. Moreover, the Authors found that anti-Hp IgG antibody levels were significantly increased in the aqueous humor and serum of patients with glaucoma reflecting the stage of the disease. Following this hypothesis, Hp may influence the pathophysiology of both glaucoma and AD by promoting platelet and platelet–leucocyte aggregation, also involved in the pathophysiology of glaucoma and AD [76].

Genetics is another factor possibly implicated in the pathophysiology of the two diseases. OPTINEURIN (OPTN) gene coding for ‘‘optineurin’’ protein is recognized as a contributory gene in adult-onset POAG [77]. Recently, a pathology study showed the presence of OPTN in neurofibrillary tangles and dystrophic neurites in AD, suggesting that OPTN may be a new common underlying risk factor involved in glaucoma and AD [77].

Finally, another mechanism supposed to bridge glaucoma and AD is autophagy. This is a cellular process involved in degradation of large intracellular components and recycling of valuable anabolic resources [78-80]. Alterations of this process have been implicated in a variety of neurodegenerative diseases including AD [80-82]. In particular, a study reported that beclin-1 is reduced in AD subjects causing alterations in the initiation and execution of autophagy [83]. Consequently, in these patients, an accumulation of the amyloid precursor protein and amyloid-beta resulting in neuronal cell death has been reported [83]. Russo *et al*. recently reported that autophagy occurs constitutively in RGC and that an acute IOP elevation can disrupt the retinal autophagic mechanism [84]. This has been confirmed by the reduced expression of microtubule-associated protein 1A/1B-light chain 3-phosphatidylethanolamine conjugate (LC3-II) and beclin-1, two specific markers of autophagy. Accordingly, pharmacological inhibition or silencing of beclin-1 induced a

blockage of autophagy causing RGC death. This suggests a neuroprotective role of this process in the retina, supporting the hypothesis that autophagy dysfunction may play a fundamental role in glaucoma and AD.

CONCLUSION

In conclusion, preclinical and clinical evidence gathered so far support the notion that POAG is a widespread neurodegenerative condition whose common pathogenetic mechanisms with other diseases, *i.e*. AD should be further investigated to shed new light on these diseases improving both the diagnosis and treatments.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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