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Mini Review

Association of Alzheimer's Disease, Chronic Glaucoma and Age-Related Macular Degeneration

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Received: March 01, 2023; **Published:** March 20, 2023

Abstract

Recent evidence has suggested a potential association between Alzheimer's disease (AD), chronic glaucoma (CGL) and age-related macular degeneration (AMD). Although several lines of evidence indicate that CGL and AMD may be associated with AD due to common pathophysiological mechanisms including progressive neurodegeneration, characteristic amyloid-β (Aβ) deposits and chronic microvascular insults, there is still no definite answer. Therefore, we conducted a mini-review to describe the findings of the AD, CGL and AMD literature. Further research, including large and well-designed prospective studies with long follow-ups, is needed to clarify this association.

Keywords: *Neurodegenerative Diseases; Alzheimer's Disease; Chronic Glaucoma; Age-Related Macular Degeneration*

Abbreviations

Aβ: Amyloid-β; AD: Alzheimer's Disease; AMD: Age-Related Macular Degeneration; APP: Amyloid Precursor Protein; CGL: Chronic Glaucoma; CSF: Cerebrospinal Fluid; IOP: Intraocular Pressure; NFT: Neurofibrillary Tangles; ONH: Optic Nerve Head; POAG: Primary Open-Angle Glaucoma; RGCs: Retinal Ganglion Cells; RPE: Retinal Pigmented Epithelium; RR: Relative Risk

Introduction

A potential association between Alzheimer's disease (AD), chronic glaucoma (CGL) and age-related macular degeneration (AMD) has been suggested [1,2].

Dementia is a group of neurodegenerative disorders that occurs in the elderly and leads to progressive deterioration of the memory and impaired cognition [3,4]. AD is the most common form of dementia [5,6] and is characterized by the accumulation of extracellular Aβ plaques and intracellular neurofibrillary tangles (NFT) consisted of hyperphosphorylated tau protein [7-11].

Glaucoma is a group of optic neuropathies that are characterized by progressive neurodegeneration of the retinal ganglion cells (RGCs) and their axons, resulting in structural changes of the optic nerve head (ONH) and visual field defects [12,13]. Elevated intraocular pressure (IOP) is a major risk factor of glaucoma [14] and primary open-angle glaucoma (POAG) is its most prevalent form worldwide [15].

AMD, a leading cause of severe and irreversible vision impairment [16,17], is a disorder that is characterized by a progressive loss of color and central vision due to neurodegenerative and neovascular changes in the macula [18].

In this mini-review, we focused on the epidemiological and experimental data in order to have an overview of the existing evidence on this particular field of research.

Association between AD and CGL: Epidemiological and experimental data

Several epidemiological studies (Table 1) revealed a higher risk of glaucoma in patients with AD [19-22], whereas one study observed an inverse association [23]. Chandra and colleagues reported a large positive and strongly significant relative risk (RR) for the association between AD and glaucoma using death certificates that had more than 20,000 participants [19]. In 2002, Bayer and colleagues published two prevalent case-control studies including 49 and 112 patients with AD respectively, concluding that there was a higher risk of glaucoma in patients with AD [20,21]. Similarly, in 2006 Tamura and colleagues in a case-control study performed in four Japanese hospitals reported a higher risk of glaucoma in patients with AD [22]. In contrast, in 2012 Ou and colleagues in a large retrospective cohort study with 63,325 cases of glaucoma reported a statistically significant inverse association between AD and glaucoma [23].

Furthermore, data from patients with AD pathology supported a link between AD and retinal ganglion cell (RGC) loss that is associated with typical glaucomatous damages [24-26] (Table 1). Moreover, Gupta and colleagues analyzing a sample of human ocular tissue with glaucoma showed that abnormal hyperphosphorylated tau-protein (by means of monoclonal antibody AT8) was increased in the posterior retina, while normal tau-protein (by means of monoclonal antibody BT2) was found in decreased concentrations in the same region [27]. Yoneda and colleagues reported that glaucoma patients had similar levels of Aβ and tau-protein in their vitreous fluid as well as in the cerebrospinal fluid (CSF) of patients with AD [28]. On the other hand, McKinnon and colleagues using experimental specimens of rat RGCs exposed to chronic ocular hypertension revealed an activation of a family of proteases entitled caspases, in particular caspase-3 and caspase-8, as well as an abnormal processing of amyloid precursor protein (APP), thus providing an additional window to the pathophysiological mechanism of glaucoma [29]. In addition, Guo and colleagues reported that Aβ is implicated in glaucoma-induced apoptosis of RGCs in experiments performed on a glaucoma animal model [30]. Furthermore, several other studies using transgenic mouse models of AD showed deposits of Aβ and tau-protein, overexpression of APP and neuronal cell death in their retina layers [31-34] (Table 1).

Association between AD and AMD: Epidemiological and experimental data

Some epidemiological studies have reported mixed results for the association between AD and AMD [35-41] (Table 2). Keenan and colleagues showed that patients with AMD do not have an increased risk of AD [35]. On the contrary, Klaver and colleagues in a prospective, population-based study in Netherlands from 1993 through 1994 adjusted for age and gender concluded that patients with advanced AMD at baseline showed an increased risk of AD [36]. In addition, Wong and colleagues in a population-based cross sectional study reported that patients with severe cognitive impairment had an increased risk of early AMD [37]. Furthermore, Pharm and colleagues reported a significant association between late AMD and cognitive impairment, but no significant association between early AMD and cognitive impairment [38]. Woo and colleagues in a case-control study conducted in a community-dwelling Korean population showed that patients with AMD had an increased risk of cognitive impairment when compared to non-AMD participants [39]. According to an explanation given by the authors this may be due to the fact that poor vision due to AMD may negatively affect the vision-associated parts of the brain cortex, thus resulting in an impairment of cognitive function [39]. An inverse association between low cognitive function and early AMD was found in a large population-based study with 2,088 participants performed by Baker and colleagues, showing the controversy on this topic [40]. Finally, Wen and colleagues in a population-based retrospective cohort study reported that compared to non-AMD participants, patients with AMD had an increased risk of AD [41].

Multiple lines of experimental evidence have indicated that AD and AMD might be associated via common molecular components [42-45] (Table 2). Johnson and colleagues reported that Aβ, the major component of the senile plaques in AD, was deposited with fragments

Study	Location	Design	Cases/controls	Exposure/Outcome	RR (95% CI)
Chandra, 1986 [19]	USA	Case-control	7,195/14,390	OAG/AD	2.60 (1.06-6.43)
Bayer, 2002 [20]†	Germany	Prevalent case-control	49/186	OAG/AD	4.70 (1.95-11.4)
Bayer, 2002 [21]†	Germany	Prevalent case-control	112/116	OAG/AD	6.41 (2.56-16.1)
Tamura, 2006 [22]	Japan	Case-control	172/176	OAG/AD	3.13 (1.67-5.85)
Ou, 2012 [23]‖	USA	Retrospective cohort	63,325/63,325	OAG/AD	0.91 (0.88-0.93)
Blanks, 1996 [24]*	USA	Experimental	9/11	AD/GCLN	NR
Parisi, 2001 [25]	Italy	Case-control	17/14	AD/NFLT	NR
Iseri, 2006 [26]	Turkey	Case-control	14/15	AD/RNFLT	NR
Gupta, 2008 [27]*	Canada	Experimental	11/10	AT8/GLAUCOMA	NR
Yoneda, 2005 [28]*	Japan	Experimental	8/13	Abeta42 & Tau/GLAUCOMA	NR
McKinnon, 2002 [29]‡	USA	Experimental	8/8	OHT/CASPACE ACTIVATION&APPC	NR
Guo, 2007 [30]‡	UK	Experimental	NR	OHT/Aβ&RGCA	NR
Ning, 2008 [31]‡	Canada	Experimental	17	AD/Aβ&APP	NR
Liu, 2009 [32]‡	USA	Experimental	NR	AD/RMDAβ	NR
Perez, 2009 [33]‡	USA	Experimental	16/13	AD/RAβPD	NR
Gasparini, 2011 [34]‡	UK	Experimental	NR	HPTAU/AV	NR

Table 1: *Study characteristics of the reviewed studies on Alzheimer's disease and chronic glaucoma.*

Abbreviations: Aβ: Amyloid-β; Abeta42: Beta-Amyloid (1-42); AD: Alzheimer's Disease; APP: Amyloid Precursor Protein; APPC: Amyloid Precursor Protein Cleavage; AT8: Monoclonal Antibody; AV: Axonal Viability; CI: Confidence Interval: GCLN: Ganglion Cell Layer Neurons; HPTAU: Hyperphosphorylated Tau; NFLT: Nerve Fiber Layer Thickness; NR: Not Reported; OAG: Open-Angle Glaucoma; OHT: Ocular Hypertension; RAβPD: Retina Aβ Plaque Deposition; RGCA: Retinal Ganglion Cell Apoptosis; RMDAβ: Retinal Microvascular Deposition of Aβ; RNFLT: Retinal Nerve Fiber Layer Thickness; RR: Relative Risk.

†: It is not clear if these studies use independent samples.

‖: 14 years of follow-up.

**: Experimental study including human eyes.*

‡: Experimental study including rat/mice eyes.

of complement C3 within drusen in eyes with AMD [42]. In addition, Dentchev and colleagues found the same deposition of Aβ in drusen of post mortem human retinas in patients with AMD [43]. Moreover, Anderson and colleagues in a sample of 152 human eyes found that Aβ deposits are most ubiquitous in eyes with moderate or high drusen loads, proposing that Aβ might be implicated with AMD [44]. Furthermore, Luibl and colleagues observed nonfibrillar amyloid oligomers in drusen, indicating that AMD might be associated with other amyloid diseases including AD [45]. Interestingly, some studies presume that both AD and AMD might share common risk factors and pathophysiological mechanisms including substantial glial reactivity, imbalanced angiogenesis, neuroinflammation and increased metabolic and oxidative stress [46-48] (Table 2). In an experimental study with mice performed by Bruban and colleagues subretinal Aβ injection caused alterations in the retinal pigmented epithelium (RPE) leading to retinal degeneration [49]. The authors concluded that targeting Aβ might be useful in developing treatments for diseases associated with retinal degeneration, such as AMD [49]. Schwaber and colleagues in a cross sectional study with autopsy ocular specimens from patients with and without AMD showed that the prevalence of AD was significantly less in AMD subjects [50].

Study	Location	Design	Cases/controls	Exposure/Outcome	RR (95% CI[b])
Kennan, 2014 [35]	UK	Cohort	65,894/7,700,000	AMD/AD	0.86 (0.67 - 1.08)
Klaver, 1999 [36]	Netherlands	Cohort	113/1,438	ARM/AD	2.10 (1.10 - 4.30)
Wong, 2002 [37]	Singapore	Cohort	448/9,286	CI[a]/ARM	1.60 (1.10 - 2.20)
Pham, 2006 [38]	Australia	Cross-sectional	50/2,984	AMD/CI[a]	3.70 (1.30 - 10.60)
Woo, 2012 [39]	Korea	Case-control	170/190	AMD/MCI	3.13 (1.86 - 5.27)
Baker, 2009 [40]	Australia	Cross-sectional	86/2,088	CF/AMD	0.81 (0.45 - 1.48)
Wen, 2021 [41]	Taiwan	Retrospective cohort	10,578/10,578	AMD/AD	1.23 (1.04 - 1.46)
Johnson, 2002 [42]*	USA	Experimental	10	Aβ/AMD	NR
Dentchev, 2003 [43]*	USA	Experimental	9/9	Aβ/AMD	NR
Anderson, 2004 [44]*	USA	Experimental	152	Aβ/AMD	NR
Luibl, 2006 [45]*	USA	Experimental	14/5	NFAO/AMD	NR
Löffler, 1995 [46]*	USA	Experimental	10	anti-tau-1 IR & anti-tau-2 IR & anti-APP IR & anti-beta-amyloid IR/ARMD	NR
Yoshida, 2005 [47]	Japan	Experimental	NR	Aβ/AMD	NR
Isas, 2010 [48]*	USA	Experimental	9/2	NFO/AMD	NR
Bruban, 2009 [49]	France	Experimental	NR	OAβ (1 - 42)/AMD	NR
Schwaber, 2020 [50]	USA	Experimental	91/66	AMD/AD	0.47 (0.22 - 1.00)

Table 2: *Study characteristics of the reviewed studies on Alzheimer's disease and age-related macular degeneration. Abbreviations: Aβ: Amyloid-β; AD: Alzheimer's Disease; AMD: Age-Related Macular Degeneration; ARM: Age-Related Maculopathy; ARMD: Age-Related Macular Degeneration; CF: Cognitive Function; CI[a]: Cognitive Impairment; CI[b]: Confidence Interval; IR: Immunoreactivity; MCI: Mild Cognitive Impairment; NFAO: Nonfibrillar Amyloid Oligomers; NFO: Nonfibrillar Oligomers; NR: Not Reported; OAβ (1 - 42); Oligomeric Form of Aβ (1 - 42); RR: Relative Risk.*

** Experimental study including human eyes.*

Conclusion

In summary, the association between AD, CGL and AMD is heterogeneous in the literature and most of the studies are small and poorly designed. Large and high-quality prospective studies with long follow-ups are needed to clarify this potential association in both directions, particular among glaucoma or AMD patients who get diagnosed with AD and AD patients with glaucoma or AMD.

Acknowledgements

None of the authors had a financial support related to this study. The authors declare that there is no conflict of interests regarding the publication of this paper. This submission has not been published elsewhere previously and it is not currently under consideration by another journal.

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Volume 14 Issue 4 April 2023