

# Alzheimer's disease and primary open-angle glaucoma: is there a connection?

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**Aim:** To present, through a thorough literature research, current and older scientific efforts to investigate the putative association between Alzheimer's disease (AD) and glaucoma, especially primary open-angle glaucoma (POAG).

**Methods:** We included in our review article epidemiological, experimental and clinical laboratory studies.

**Results:** While many authors support the existence of a strong correlation between the AD and POAG, based on epidemiological, genetic and immunohistochemical data, others present contradictory results, leaving the issue unresolved.

**Conclusion:** Further research, probably targeted towards genetic parameters and based on large, multicenter studies has yet to be conducted. It is the authors' opinion however, that the existing data already justify the need for at least some degree of elevated clinical alertness for the occurrence of AD in patients with glaucoma and of glaucoma in patients with AD.

**Keywords:** Alzheimer's disease, primary open-angle glaucoma, amyloid beta, apolipoprotein E, cerebrospinal fluid pressure, review article

## Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder which is one of the main causes of dementia worldwide. It gradually affects all fields of cognition, including short and long-term memory, executional capacity and behavior. Unfortunately, despite advanced and intense research, no definitive therapy is currently available.<sup>1</sup> Glaucoma, one of the leading causes of blindness today,<sup>2,3</sup> with 60 million persons affected and 8.4 million bilaterally blinded by the disease,<sup>3</sup> is also a neurodegenerative disorder, characterized by degeneration of the retinal ganglion cells. The attempt to link these two disorders has been the focus of much research in recent years. The evidence-based establishment of such a connection would have a lot to offer in terms of increased clinical awareness, prophylaxis and early diagnosis of dementia for glaucoma patients and vice versa; it would also allow novel therapeutic approaches based on the knowledge of common etiology or causal relationship between the two conditions.

In this review article, we have examined important recent and older articles dealing with the subject, both epidemiological/clinical as well as experimental, in an effort to clarify the problem and highlight the need for further research in this direction. We have focused our interest on primary open-angle glaucoma (POAG), which is the most common form of the disease, and which, due to its unknown etiology, is most likely to share common ground with AD.

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## Studies

### Epidemiological studies

Chandra et al<sup>4</sup> reported, based on a register study of US death certificates, an increased prevalence of glaucoma among patients who died bearing the official diagnosis of senile and presenile dementia. More recently, Bayer et al<sup>5</sup> announced a higher prevalence of glaucoma among AD patients (25.9%) in comparison to the prevalence observed in a control group of non-AD individuals (5.2%). Tamura et al<sup>6</sup> reached the same conclusion based on a larger prospective study sample, comprised of 172 AD and 176 control individuals. The reverse relationship, that of an augmented occurrence of AD among glaucomatous patients, has also been investigated. Recently, Yochim et al<sup>7</sup> found that more than 40% of a 41-person sample of aged glaucomatous patients showed cognitive impairment, in the form of either memory impairment or executive dysfunction, but without an official diagnosis of AD. This fact has implications in the ability of these patients to comply with an adequate antiglaucoma regimen. However, the relationship between dementia and glaucoma could not be proven in a large study (sample size more than 11,000 subjects) performed by Kessing et al,<sup>8</sup> which however had the major disadvantage of being a retrospective register-based study. Similarly, Bach-Holm et al,<sup>9</sup> in a recently published register-based study with a 20-year follow-up that comprised 69 normal-tension glaucoma patients reported a lack of correlation of this disorder with AD, as none of the enlisted patients developed AD.

### Experimental studies on animals

As a disorder in the production and deposition of Amyloid-beta ( $A\beta$ ) in the brain, amyloid plaques are characteristics of Alzheimer's disease. Many researchers have focused their research on the role of  $A\beta$  in the development of glaucoma. Guo et al,<sup>10</sup> using a rat model experimental study, induced augmented intraocular pressure in male rats and found augmented amyloid beta aggregation in the affected retinal ganglion cells, a finding missing in the related cells of the contralateral, non-affected eyes. In a similar, more recent study, Kipfer-Kauer et al<sup>11</sup> managed to detect an amyloid regulating protein, called amyloid precursor protein (APP), as well as  $A\beta$  in augmented concentrations in the optic nerves and retinal ganglion cells of rat eyes in which ocular hypertension was surgically induced. McKinnon<sup>12</sup> also worked with a rat glaucoma experimental model, elucidating the role of apoptotic cell death through activation of a family of proteases, called caspases. These proteolytic enzymes (especially caspase-3 and caspase-8) act on APP to cause

the production of neurotoxic fragments, which include  $A\beta$ , thus providing an extra pattern of common etiology between AD and glaucoma at the cellular level. Vickers<sup>13</sup> has also emphasized the role of cellular damage and cellular reaction to stress in the development of AD and glaucoma; He focused his studies on the neurofilament triplet, a group of cytoskeletal proteins accumulated in cases of damage to the larger retinal ganglion cells.

### Clinical-laboratory studies on humans

A very interesting study that added a lot to the elucidation of the putative association between Alzheimer's disease and glaucoma was conducted by Gupta et al.<sup>14</sup> The researchers used human ocular tissue specimens gained during glaucoma operations, and compared their immunohistochemical characteristics to those of living and postmortem control tissue specimens. They found that patients with unregulated intraocular pressure had decreased concentrations of normal tau-protein (BT2) and increased presence of abnormal hyperphosphorylated tau-protein molecules (AT8), especially within the posterior retina; such molecules can also be detected in the cerebrospinal fluid (CSF) of AD patients. In another clinical-laboratory study, Yoneda et al<sup>15</sup> measured the  $A\beta$  42 and tau-protein levels of the vitreous fluid in patients with retinal pathologies undergoing vitrectomy (including glaucomatous patients) and compared them to those of control patients. Patients with glaucoma had decreased levels of  $A\beta$  and increased levels of tau-proteins in their vitreous fluid. This finding is possibly linked to the decreased levels of  $A\beta$  and increased levels of tau-proteins in the CSF of AD patients.

Another possible link between AD and glaucoma lies in the CSF pressure, which appears to be decreased in AD patients, a fact also observed among POAG patients.<sup>16</sup> Ren et al, in two recent studies,<sup>17,18</sup> which recruited patients with high-tension glaucoma, normal-tension glaucoma, patients with intraocular pressure without glaucoma and healthy subjects, highlighted the importance of the translamina-cribrosa pressure difference in the development of at least one of the characteristic optic nerve damages of glaucoma, loss of neuroretinal rim (the others being deepening of the optic cup and parapapillary atrophy), and of the subsequent visual deficits. The translamina-cribrosa pressure difference may be a combination of normal intracranial/intraocular pressure and decreased CSF pressure or of an elevated intracranial/intraocular pressure and normal CSF pressure. Berdahl and Allingham<sup>19</sup> also highlighted the importance of reduced CSF pressure in the pathogenesis of glaucoma, in addition

to the significance of elevated intracranial pressure in cases of high-tension glaucoma. Elevated intracranial pressure is also considered as a characteristic finding in AD. Wostyn et al<sup>22</sup> addressed the quite complex issue of CSF pressure, AD and glaucoma: they correlated early stages of AD with elevated CSF pressure and later stages with decreased CSF pressure. They also highlighted the importance of a high trans-lamina-cribrosa pressure difference in the development of glaucoma.<sup>20–22</sup>

## Apolipoprotein E gene and glaucoma

An additional field of research into links between AD and glaucoma focuses on the apolipoprotein (APOE) gene and its variations. The gene is implicated in brain cholesterol and amyloid metabolism, and its APOE-ε4 variation is regarded as one of the major predisposing factors for the development of AD.<sup>23</sup> It is also responsible for decreased capacity of nerve cells in response to stress and for delayed rehabilitation after stroke or head trauma.<sup>24–26</sup> This is the reason that many scientists have worked on the putative association of the gene with glaucoma. Zetterberg et al<sup>27</sup> focused on the issue in a study of over 400 subjects and found no such correlation. Tamura et al,<sup>6</sup> Ressiniotis et al,<sup>28</sup> and Lake et al<sup>29</sup> in older similar studies also obtained negative results, even for normal tension glaucoma, which would theoretically leave more “room” for genetic factors like APOE to work as glaucoma precipitating factors.

Al-Dabbagh et al,<sup>30</sup> on the contrary, in a study performed on 230 Saudi individuals, found a positive correlation between the Apoe-ε4 allele and the development of primary open-angle glaucoma, and, in addition, found a protective role of the ε-3 allele against the disease. Saglar et al<sup>31</sup> also performed a genetic study on 75 patients with POAG and 119 control individuals and found no correlation between the polymorphisms of the APOE, tumor suppressor protein 53 (p53) and cyclin-dependent kinase inhibitor 1A (p21) genes on one hand and POAG on the other. However, Lam and associates<sup>32</sup> concluded in a genetic study performed on 400 Chinese individuals that APOE-ε4 is associated with glaucoma, but by acting as a protective factor against it.

Pseudoexfoliation glaucoma is a form of secondary glaucoma, which is characterized by ocular accumulation of fibrils containing amyloid-related proteins, thus probably sharing common features with AD. Krumbiegel et al<sup>33</sup> however, in a meta-analysis comprising two European (one German and one Italian) cohorts, with over 1000 participants, found a negative correlation between APOE polymorphisms and this disorder.

## Conclusion

Many important studies have supported the connection between AD and POAG. These data derive from epidemiological, experimental and clinical laboratory studies. These results, however, are contradicted by a series of other equally significant studies: this shows that the etiology of both AD and POAG is complex and warrants further focused investigation.

The existing data justify an elevated level of clinical awareness for the diagnosis of glaucoma in AD patients and vice versa. Hopefully, future research will shed light on the issue to the benefit of these two large categories of patients.

## Disclosure

The authors report no conflicts of interest in this work.

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