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P Wostyn, K Audenaert and P P De Deyn

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P Wostyn,[1] K Audenaert,[2] P P De Deyn[3,4]

[1] Department of Psychiatry, PC Sint-Amandus, Beernem, Belgium; [2] Department of Psychiatry, Ghent University Hospital, Ghent, Belgium; [3] Department of Neurology and Memory Clinic, Middelheim General Hospital (ZNA), Antwerp, Belgium; [4] Laboratory of Neurochemistry and Behavior, Institute Born-Bunge, University of Antwerp, Antwerp, Belgium

Correspondence to:
Dr P Wostyn, Department of Psychiatry, PC Sint-Amandus, Reigerlostraat 10, 8730 Beernem, Belgium; wostyn.peter@skynet.be

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ABSTRACT

Evidence of a link between Alzheimer's disease (AD) and glaucoma has emerged from studies showing that patients with AD may have a significantly increased rate of glaucoma occurrence. In addition, it has been reported that patients with AD exhibit optic nerve degeneration and loss of retinal ganglion cells. In spite of intensive research, the clinical and genetic relationships between AD and glaucoma remain obscure. It is unclear whether the clinical correlation between the two diseases might be due to shared risk factors or the influence of one disorder on the other. Interestingly, certain observations may provide a clue towards a better understanding of the high rate of comorbidity reported between AD and glaucoma. In this article, we hypothesise that there may be a causal relationship between AD and glaucoma that may be explained by decreased cerebrospinal fluid pressure (CSFP) in patients with AD. A very recent study reported the intriguing new observation that mean CSFP was 33% lower in subjects with primary open-angle glaucoma than that of non-glaucomatous controls. It was noted that this observation supports the concept that an abnormal high trans-lamina cribrosa pressure difference, whether the result of elevated intraocular pressure, reduced CSFP, or both, plays an important role in glaucomatous optic nerve damage. Interestingly, it was also reported that a substantial proportion of AD patients have very low CSFP. Therefore, we hypothesise that an abnormal high trans-lamina cribrosa pressure difference may explain why patients with AD have a greater risk for developing glaucoma.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterised by cognitive and memory deterioration, as well as changes in personality, behavioural disturbances and an impaired ability to perform activities of daily living.[1] AD is known to be the most common form of dementia and is a major public health problem throughout the world.[2 3] In addition to synaptic degradation and extensive neuronal cell loss, neuropathological characteristics of AD include extracellular senile plaques containing β-amyloid (Aβ) derived from β-amyloid precursor protein (APP) after sequential cleavage by β-secretase and γ-secretase, and intracellular neurofibrillary tangles caused by abnormally phosphorylated tau protein.[4–6] Early-onset familial AD caused by mutations in genes encoding APP, presenilin-1 and presenilin-2 accounts for less than 5% of the total number of AD cases.[2] The majority of AD cases are sporadic with late onset and seem to result from a complex interaction of multiple genetic and environmental factors.[2] An important genetic risk factor for late-onset AD is the ε4 allele of the apolipoprotein E (APOE) gene located on chromosome 19.[7 8] The pathogenesis of AD is complex, and involves many molecular, cellular and physiological pathologies.[9] Aβ is widely believed to be central to the pathogenesis in AD.[9]

Glaucoma is one of the leading causes of vision loss worldwide.[8] Open-angle glaucoma (OAG), the most common form of glaucoma, is characterised by a progressive loss of retinal ganglion cells (RGCs) and atrophy of the optic nerve, resulting in loss of visual field.[8 10] Mechanical and vascular theories for the pathogenesis of glaucomatous optic neuropathy have been proposed.[10] Elevated intraocular pressure (IOP) is a strong risk factor, but a subset of glaucoma patients has normal IOP and is designated normal tension glaucoma.[8 10] Clearly, factors other than IOP, including genetic factors, are likely to be involved in RGC death in glaucoma.[11] Some studies have implicated the ε4 allele of the APOE gene in the pathophysiology of OAG, but the data are conflicting.[8 12 13]

There is a growing body of evidence demonstrating a link between AD and glaucoma. However, the nature of this link remains obscure. Interestingly, recently published research may provide a clue towards a better understanding of the high rate of comorbidity reported between AD and glaucoma. In this article, we hypothesise that there may be a causal relationship between AD and glaucoma that may be explained by decreased cerebrospinal fluid pressure (CSFP) in patients with AD. Supportive evidence for this hypothesis is reviewed based on a PubMed literature search for the period 1986 to July 2008. The search keywords, used in different combinations, were "Alzheimer's disease", "Glaucoma" and "Cerebrospinal fluid pressure". Fifteen articles were selected. In addition, other relevant articles were identified from supplemental searches.

SIMILARITIES BETWEEN AD AND GLAUCOMA

It is intriguing to note that AD and glaucoma have many common features.[8] Both are slow and chronic neurodegenerative disorders with a strong age-related incidence.[14 15] Studies consistently report decreased levels of β-amyloid (1–42) and increased levels of tau in cerebrospinal fluid (CSF) from AD patients in comparison with healthy subjects.[16 17] Recently, Yoneda *et al*[17] suggested the possibility of a role for β-amyloid (1–42) and tau in the pathogenesis of glaucoma and diabetic retinopathy, having found significantly decreased levels of β-amyloid (1–42) and significantly increased levels of tau in the vitreous fluid from patients with these disorders in comparison with the levels in a control group. Their findings suggested that

the neurodegeneration processes in these ocular diseases might share, at least in part, a common mechanism with AD.[17] It was also demonstrated recently that abnormal tau AT8 is present in human glaucomas with uncontrolled elevated IOP.[18] Furthermore, there is evidence of a build-up of Aβ in RGCs in experimental rat glaucoma.[19] Activation of caspases and abnormal APP processing, which includes production of Aβ, are important events in AD.[19] McKinnon and colleagues[19] detected a similar situation in experimental glaucoma. Indeed, in their study using a chronic ocular hypertensive rat glaucoma model, the authors found that caspase-3 is activated in RGCs, where it cleaves APP to produce neurotoxic fragments that include Aβ.[19] This suggested a new hypothesis for RGC death in glaucoma involving chronic Aβ neurotoxicity, mimicking AD at the molecular level.[11] A study published by Guo *et al* in 2007[14] provided evidence that targeting Aβ and blocking its effects with combination therapy may represent an effective treatment strategy in glaucoma. Further evidence of a link between AD and glaucoma has emerged from studies showing that patients with AD exhibit optic nerve degeneration and loss of RGCs.[20 21] In addition, other studies found a significantly increased occurrence rate of glaucoma among patients with AD.[8 22] In a study based in nursing homes in Germany, the prevalences of glaucoma (as defined by characteristic optic nerve or visual field changes) were reported to be 25.9% in patients with AD and 5.2% in controls.[22] In addition, the occurrence rate of ocular hypertension with normal visual fields and normal optic nerve heads in patients with AD was 0% compared with a prevalence of about 7% in the control subjects.[22] The authors assumed that the optic nerve was less resistant to elevated IOP levels in AD patients.[22] In another study, Tamura *et al*[8] found that the prevalence of OAG in Japanese patients with AD was 23.8%, which was significantly higher than that of the control subjects (9.9%). Furthermore, there was no significant difference between IOPs in AD patients with OAG and without OAG, and almost all AD patients with OAG had normal tension.[8] The authors concluded by suggesting that careful attention should be given to the potential for OAG in AD patients, stressing the importance of not giving the impression to non-ophthalmic trained physicians or clinicians that OAG would be manifest through visual disturbance.[8]

In spite of intensive research, the clinical and genetic relationships between AD and glaucoma remain obscure.[8] It is unclear whether the clinical correlation between the two diseases might be due to shared risk factors or the influence of one disorder on the other. There are several candidate common risk factors. For example, Tamura *et al*[8] evaluated the APOE ε4 allele as a common risk factor for AD and OAG. The percentage of AD patients with OAG who carried an APOE ε4 allele was not significantly different than that of AD patients without OAG.[8] Their results suggested that APOE ε4 polymorphism may not be a common risk factor predisposing to both disorders.[8] Recently, *Helicobacter pylori* infection has also been suggested to be involved in the pathogenesis of both AD and glaucoma.[23] To investigate whether primary open-angle glaucoma (POAG) is associated with increased risk of developing AD, Kessing *et al*[24] carried out a nationwide case register study comparing the rate of subsequent AD for patients with POAG (including normal tension glaucoma) with the rate for patients with primary angle-closure glaucoma (PACG), cataract and osteoarthritis (OA) and with the rate for the general population. All patients included in the study were identified at hospital admission or outpatient contact during the period from 1977 to 2001 in Denmark.[24] The authors did not confirm the hypothesis that patients with POAG have increased risk of developing AD.[24] Indeed, patients with POAG did not have an increased rate of subsequent AD compared with patients with PACG, cataract or OA or when compared with the general population.[24]

PRESENTATION OF THE HYPOTHESIS

As noted above, we hypothesise that there may be a causal relationship between AD and glaucoma that may be explained by decreased CSFP in patients with AD. In a retrospective case–control study, Berdahl *et al*[25] reported the intriguing new observation that mean CSFP was 33% lower in subjects with POAG (9.2 mmHg) than that of non-glaucomatous controls (13.0 mmHg; $p<0.00005$). Subjects were considered to have POAG if they were diagnosed with POAG by a glaucoma specialist, had characteristic optic nerve changes, and had visual field loss consistent with glaucoma.[25] The criteria did not include IOP, because POAG occurs across the entire spectrum of IOP.[25 26] The authors noted that their observation supports the concept that an abnormal high trans-lamina cribrosa pressure difference (a pressure difference across the lamina cribrosa), whether the result of elevated IOP, reduced CSFP, or both, plays an important role in glaucomatous optic nerve damage.[25] The lamina cribrosa forms the bottom of the optic cup in the optic nerve head (optic disc) and acts as a pressure barrier between the intraocular pressure space and the retrobulbar CSF pressure space.[10 27] Normally, the IOP ranges from 10 to 21 mmHg, whereas the CSFP ranges from 5 to 15 mmHg (or 68 to 204 mmH_2O).[25] From a mechanical perspective, a similar posteriorly directed force is caused by either a lower pressure on the CSF side of the lamina or a higher pressure on the intraocular side.[25] Berdahl *et al*[25] found that IOP, CSFP and the trans-lamina cribrosa pressure difference all correlated with cup-to-disc ratio. Multivariate analysis showed that larger cup-to-disc ratio (an important parameter in the assessment of disc damage in glaucoma) was associated with lower CSFP.[25] Importantly, the observation of Berdahl *et al*[25] may also shed new light on the link between AD and glaucoma. Silverberg *et al*[28] reported in 2006 on CSFP in patients with AD. In a clinical trial of low-flow CSF shunting for AD, AD subjects by National Institutes of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association criteria were carefully screened to exclude those with normal pressure hydrocephalus (NPH).[28] As a final exclusion prior to shunt implantation, CSFP was measured supine under general anaesthesia via the implanted ventricular catheter.[28] During the initial implantation procedure, seven of the 181 subjects (3.9%) with no clinical or radiographic signs of NPH had an opening CSFP >200 mmH_2O.[28] These subjects were withdrawn from the remainder of the study, because of probable associated early NPH.[28] For this AD-elevated CSFP group, the mean CSFP was 249 (SD 20) mmH_2O.[28] AD patients with elevated CSFP were significantly younger and significantly less demented on the Mattis Dementia Rating Scale (MDRS) than those without elevated CSFP.[28] The AD group without elevated CSFP consisted of 174 subjects (the remaining 96.1%).[28] Mean opening CSFP in this group was 103 (SD 47) mmH_2O, which was statistically significantly lower than in the AD-elevated CSFP group and a somewhat younger non-demented control group of subjects with Parkinson's disease (140 (SD 60) mmH_2O).[28 29] The distribution of CSFP in all AD subjects is shown in fig 1. Remarkably, the frequency histogram of the CSFP distribution shows a substantial proportion of AD patients with very low CSFP. Indeed, it could be argued that there are really two subgroups of AD patients within the group without elevated

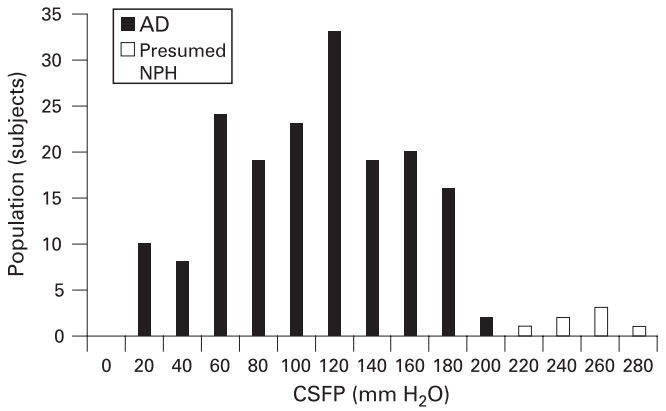

Figure 1 Frequency histogram showing the distribution of cerebrospinal fluid pressure (CSFP) in all subjects with Alzeimer's disease (AD). Reproduced with permission from Silverberg *et al*.[28] NPH, normal pressure hydrocephalus.

CSFP: those with nearly normal CSFP and those with much lower CSFP (G. Silverberg, personal communication, 2008). An unexpected finding of this study was the relatively high proportion of subjects (>30%) with moderate to severe dementia as measured by MDRS total scores below 100, despite inclusion–exclusion criteria designed to capture subjects with mild to moderate dementia (Mini-Mental State Examination score between 15 and 24, inclusive).[28 30] Cerebral atrophy associated with moderate to severe AD could be assumed to be the cause of the lower CSFP (G. Silverberg, personal communication, 2008). However, this has not been specifically investigated in this study (G. Silverberg, personal communication, 2008). Given the observation that a substantial proportion of AD patients has very low CSFP,[28] and given that a reduction in CSFP may produce an abnormal high trans-lamina cribrosa pressure difference leading to glaucomatous damage,[25 26] we hypothesise that such a high pressure difference may explain why patients with AD have a greater risk for developing glaucoma. This obviously needs to be confirmed by future research. In addition, it should be stressed that it may be possible to hypothesise other factors that also might explain the link between AD and glaucoma.

TESTING THE HYPOTHESIS

To assess whether decreased CSFP is associated with OAG in patients with AD, CSFP could be compared between AD patients with OAG, AD patients without OAG, and appropriate controls. A significantly lower CSFP in AD patients with OAG compared with that in AD patients without OAG would support our hypothesis.

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REFERENCES

1. **Bullock R,** Hammond G. Realistic expectations: the management of severe Alzheimer disease. *Alzheimer Dis Assoc Disord* 2003;**17**(Suppl 3):S80–5.
2. **Rocchi A,** Pellegrini S, Siciliano G, *et al*. Causative and susceptibility genes for Alzheimer's disease: a review. *Brain Res Bull* 2003;**61**:1–24.
3. **Sloane PD,** Zimmerman S, Suchindran C, *et al*. The public health impact of Alzheimer's disease, 2000–2050: potential implication of treatment advances. *Annu Rev Public Health* 2002;**23**:213–31.
4. **Selkoe DJ.** Alzheimer's disease: genes, proteins, and therapy. *Physiol Rev* 2001;**81**:741–66.
5. **Sun X,** He G, Qing H, *et al*. Hypoxia facilitates Alzheimer's disease pathogenesis by up-regulating BACE1 gene expression. *Proc Natl Acad Sci U S A* 2006;**103**:18727–32.
6. **de Quervain DJ,** Poirier R, Wollmer MA, *et al*. Glucocorticoid-related genetic susceptibility for Alzheimer's disease. *Hum Mol Genet* 2004;**13**:47–52.
7. **Horsburgh K,** McCarron MO, White F, *et al*. The role of apolipoprotein E in Alzheimer's disease, acute brain injury and cerebrovascular disease: evidence of common mechanisms and utility of animal models. *Neurobiol Aging* 2000;**21**:245–55.
8. **Tamura H,** Kawakami H, Kanamoto T, *et al*. High frequency of open-angle glaucoma in Japanese patients with Alzheimer's disease. *J Neurol Sci* 2006;**246**:79–83.
9. **LaFerla FM.** Calcium dyshomeostasis and intracellular signalling in Alzheimer's disease. *Nat Rev Neurosci* 2002;**3**:862–72.
10. **Wostyn P,** Audenaert K, De Deyn PP. Alzheimer's disease-related changes in diseases characterized by elevation of intracranial or intraocular pressure. *Clin Neurol Neurosurg* 2008;**110**:101–9.
11. **McKinnon SJ.** Glaucoma: ocular Alzheimer's disease? *Front Biosci* 2003;**8**:s1140–56.
12. **Mabuchi F,** Tang S, Ando D, *et al*. The apolipoprotein E gene polymorphism is associated with open angle glaucoma in the Japanese population. *Mol Vis* 2005;**11**:609–12.
13. **Lake S,** Liverani E, Desai M, *et al*. Normal tension glaucoma is not associated with the common apolipoprotein E gene polymorphisms. *Br J Ophthalmol* 2004;**88**:491–3.
14. **Guo L,** Salt TE, Luong V, *et al*. Targeting amyloid-beta in glaucoma treatment. *Proc Natl Acad Sci U S A* 2007;**104**:13444–9.
15. **Wostyn P.** Can chronic increased intracranial pressure or exposure to repetitive intermittent intracranial pressure elevations raise your risk for Alzheimer's disease? *Med Hypotheses* 2004;**62**:925–30.
16. **Engelborghs S,** De Vreese K, Van de Casteele T, *et al*. Diagnostic performance of a CSF-biomarker panel in autopsy-confirmed dementia. *Neurobiol Aging* 2007;**29**:1143–59.
17. **Yoneda S,** Hara H, Hirata A, *et al*. Vitreous fluid levels of beta-amyloid((1–42)) and tau in patients with retinal diseases. *Jpn J Ophthalmol* 2005;**49**:106–8.
18. **Gupta N,** Fong J, Ang LC, *et al*. Retinal tau pathology in human glaucomas. *Can J Ophthalmol* 2008;**43**:53–60.
19. **McKinnon SJ,** Lehman DM, Kerrigan-Baumrind LA, *et al*. Caspase activation and amyloid precursor protein cleavage in rat ocular hypertension. *Invest Ophthalmol Vis Sci* 2002;**43**:1077–87.
20. **Hinton DR,** Sadun AA, Blanks JC, *et al*. Optic-nerve degeneration in Alzheimer's disease. *N Engl J Med* 1986;**315**:485–7.
21. **Blanks JC,** Hinton DR, Sadun AA, *et al*. Retinal ganglion cell degeneration in Alzheimer's disease. *Brain Res* 1989;**501**:364–72.
22. **Bayer AU,** Ferrari F, Erb C. High occurrence rate of glaucoma among patients with Alzheimer's disease. *Eur Neurol* 2002;**47**:165–8.
23. **Kountouras J,** Zavos C, Gavalas E, *et al*. Normal-tension glaucoma and Alzheimer's disease: Helicobacter pylori as a possible common underlying risk factor. *Med Hypotheses* 2007;**68**:228–9.
24. **Kessing LV,** Lopez AG, Andersen PK, *et al*. No increased risk of developing Alzheimer disease in patients with glaucoma. *J Glaucoma* 2007;**16**:47–51.
25. **Berdahl JP,** Allingham RR, Johnson DH. Cerebrospinal fluid pressure is decreased in primary open-angle glaucoma. *Ophthalmology* 2008;**115**:763–8.
26. **Pasquale LR.** Low intracranial pressure: a tipping point in our understanding of primary open-angle glaucoma? *Ophthalmology* 2008;**115**:761–2.
27. **Jonas JB,** Berenshtein E, Holbach L. Anatomic relationship between lamina cribrosa, intraocular space, and cerebrospinal fluid space. *Invest Ophthalmol Vis Sci* 2003;**44**:5189–95.
28. **Silverberg G,** Mayo M, Saul T, *et al*. Elevated cerebrospinal fluid pressure in patients with Alzheimer's disease. *Cerebrospinal Fluid Res* 2006;**3**:7.
29. **Silverberg GD,** Huhn S, Jaffe RA, *et al*. Downregulation of cerebrospinal fluid production in patients with chronic hydrocephalus. *J Neurosurg* 2002;**97**:1271–5.
30. **Silverberg GD,** Mayo M, Saul T, *et al*. Continuous CSF drainage in AD. Results of a double-blind, randomized, placebo-controlled study. *Neurology* 2008;**71**:202–9.