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Alzheimer's disease and glaucoma: Is there a causal relationship?

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Competing Interest

None declared.

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 occurrence rate of glaucoma. 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 hypothesize 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 compared with that of nonglaucomatous 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 hypothesize that an abnormal high trans-lamina cribrosa pressure difference may explain why patients with AD have a greater risk for developing glaucoma.

Text

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive and memory deterioration, as well as changes in personality, behavioral 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 ($A\beta$) 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 the APP, presenilin-1, and presenilin-2 genes 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 epsilon 4 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] $A\beta$ 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 characterized 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 $\epsilon 4$ allele of the APOE gene in the pathophysiology of OAG, but conflicting data exists.[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, lately 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 hypothesize 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 ALZHEIMER’S DISEASE 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] Lately, it was also demonstrated that abnormal

tau AT8 is present in human glaucomas with uncontrolled elevated IOP.[18] Furthermore, evidence exists of build-up of A β in RGCs in experimental rat glaucoma.[19] Activation of caspases and abnormal APP processing, which includes production of A β , 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 A β . [19] This suggested a new hypothesis for RGC death in glaucoma involving chronic A β neurotoxicity, mimicking AD at the molecular level.[11] A study published by Guo et al. in 2007 [14] provided evidence that targeting A β 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 nursing home based study 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 to a prevalence of about 7% in the control subjects.[22] The authors assumed the optic nerve to be 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 showed 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 ϵ 4 allele as a common risk factor for AD and OAG. The percentage of AD patients with OAG who carried an APOE ϵ 4 allele was not significantly different than that of AD patients without OAG.[8] Their results suggested that APOE ϵ 4 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 to patients with PACG, cataract, or OA or when compared with the general population.[24]

PRESENTATION OF THE HYPOTHESIS

As noted above, we hypothesize that there may be a causal relationship between AD and glaucoma that may be explained by decreased cerebrospinal fluid pressure 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) compared with that of nonglaucomatous 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 mmH₂O).[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 anesthesia 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 mmH₂O.[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 ± 20 mmH₂O.[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 ± 47 mmH₂O, which was statistically significantly lower when compared to the AD-elevated CSFP group and a somewhat younger non-demented control group of subjects with Parkinson's disease (140 ± 60 mmH₂O).[28,29] The distribution of CSFP in all AD subjects is shown in Figure 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 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 ($>30\%$) proportion of subjects 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 hypothesize 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 hypothesize 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 in AD patients with OAG with that in AD patients without OAG. 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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Histogram CSFP Across Population

