TITLE:

STRUCTURAL MAGNETIC RESONANCE NEUROIMAGING OF THE PARIETAL LOBE IN PRIMARY OPEN ANGLE GLAUCOMA

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KEY WORDS: PARIETAL LOBE; GLAUCOMA

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ABSTRACTS:

Objective:
There has been increasing number of evidence linking primary open angle glaucoma and Alzheimer's disease (AD). Both diseases are chronic, neurodegenerative, and progressive in nature associated with irreversible neuronal cell loss. Aside from medial temporal atrophy, parietal lobe atrophy is observed in patients with AD, particularly early onset AD. This is often best seen on the interhemispheric surface of the parietal lobe by examining the posterior cingulate sulcal and parieto-occipital sulcal size. The objective of the study is to determine if the increase incidence of parietal lobe atrophy observed in AD patients using Koedam Visual Rating is also present among patients with POAG.

Materials and Methods:
A comparative cross sectional study was carried out on POAG patients and controls using MR Neuroimaging. 55 patients (28 Male, 27 Female; Mean age: 62.0 years old) and 54 controls (30 Male, 24 Female, Mean age: 56.0 years old) underwent T1-Weighted MPRAGE. Two radiologists assessed the degree of parietal lobe atrophy using the Koedam's posterior atrophy visual rating (PA Score) based on sagittal, axial and coronal views. (GRADE 0=No atrophy; GRADE 1=Mild widening of the sulci without evident volume loss of the gyri; GRADE 2=Substantial widening of the sulci and volume loss of the gyri; GRADE 3=Severe end stage atrophy). The PA scores were analyzed and compared between the two groups. The inter-rater agreement was also evaluated using Cohen's kappa coefficient.

Results
The mean score of the POAG group was 0.92 (range 0-3; SD 0.792) and the mean score of the control group was 0.68 (range 0-2; SD 0.827). The T-Test analysis showed that there was no difference of the PA score between POAG patients and controls (p 0.242). The inter-observer agreement was statistically substantial/good with kappa value of 0.67.

Conclusion:
There was no increase frequency of parietal lobe atrophy among patient with POAG when compared to controls based on Koedam Visual Rating (PA score). We suggest further advanced MRI neuroimaging study, such as Diffusion Tensor Imaging, in looking at minute changes, which may detect the difference between the two groups.

INTRODUCTION:

Glaucoma is one of the leading causes of irreversible blindness and affects approximately 79.6 million people. Primary open angle glaucoma (POAG) is the commonest type of glaucoma that is characterized by changes in the optic disc and visual field defects. Elevated intraocular pressure (IOP) is considered the prime factor responsible for the glaucomatous optic neuropathy involving death of retinal ganglion cells and their axons. However a high percentage of patients have normal IOP. Since the elevated IOP may not be the primary cause of neuronal death in these patients, alternative mechanisms are being studied.

Alzheimer's disease (AD), the leading cause of dementia, has an age-standardized prevalence rate of 5-7% for those aged >60 years. Although AD and POAG have been established as two distinct pathological entities, there are similarities in the pathophysiology. Both POAG and AD are neurodegenerative, chronic and progressive in nature, with irreversible neuronal cell loss. Furthermore, both primarily affect the elderly and the progressive debilitating course of both diseases has tremendous implications on the aging population.

A number of possible common mechanisms linking the two diseases have come to light recently. With regards to structural brain imaging, there have not been many studies performed to link between the two entities. Interestingly, the role of parietal lobe of the brain in the development of AD has recently beginning to attract attention and it is clearly involved in early stage of AD as an imaging biomarkers. We would like to see if similar changes could be observed in patients with POAG to substantiate the link between the two. If glaucoma and AD share the same neuropathogenesis, the treatment for AD may be beneficial to patient with POAG and this potentially influences the current approach to treat patient with POAG.

Problem statement.

POAG is currently treated only with IOP lowering drugs and even with adequate control of IOP, it is known to progress in many patients. However, more and more literatures demonstrate similarities between POAG and AD, suggesting that POAG is a neurodegenerative disease similar to AD. However, no studies has been done

specifically to investigate the parietal lobe atrophy as one of the important biomarkers in AD among patients with POAG, which by proving this will strengthen the evidence that POAG and AD are of same entities.

Hypothesis

Null hypothesis: There is no parietal lobe atrophy in patient with POAG.

Alternate hypothesis: There is parietal lobe atrophy among patient with POAG.

Research question:

Is there any parietal lobe atrophy among patients with POAG as compared to the normal population?

Literature review

POAG AND AD:

The epidemiological studies have reported an increased comorbidity with POAG and AD (Bayer at al., 2012, Tamura et al., 2006). Both are slow and chronic neurodegenerative disorders with a strong age-related incidence (Guo et al., 2007, Wostyn 2004). Like AD, amyloid-β (Aβ) is one of the key histopathological findings in POAG. In animal study, Aβ has been found to be a prominent finding in retinas of glaucomatous animal models (Guo et al., 2007, McKinnon et al., 2002, Kipfer-Kauer et al., 2010, Goldblum et al., 2007). Some of the aforementioned studies have also found strong evidence of increased APP cleavage, which is understood to be a key mechanism in Aβ formation and apoptotic neuronal cell loss in AD (Guo et al., 2007, McKinnon et al., 2002, Goldblum et al., 2007). There is also accumulating evidence of increased retinal Aβ in AD. Recently, a study in Alzheimer's transgenic mice (AD-Tg) demonstrated significantly increased retinal Aβ plaques (Perez et al., 2009, Liu et al., 2009). These plaques were not observed in the non-Tg mice. Furthermore, Aβ plaques were detected earlier in the retina than in the brain, and accumulated with disease progression. In humans, Aβ plaques were also detected in postmortem retinas of AD patients, but not in age-matched controls (Koronyo-Hamaoui et al., 2011). Overall, these studies suggest strong evidence of increased retinal Aβ in both glaucoma and AD. As Aβ is detectable at an early stage in the course of both glaucoma and AD, it may have a key role in inducing retinal neurotoxicity. Interestingly, phosphorylated tau protein, which has been implicated in the amyloid

cascade hypothesis of AD was also detected in the RNFL of AD-Tg mice, adversely affecting axonal growth (Gasparinie et al., 2011). In addition, abnormally phosphorylated tau protein has also been found to be significantly increased in the human glaucomatous retina, particularly in the horizontal cells (Gupta et al., 2008). Studies consistently report decreased levels of Aβ and increased levels of tau in cerebrospinal fluid from AD patients in comparison with healthy subjects (Engelborghs et al., 2008, Yoneda et al., 2005). Recently, it was suggested that the possibility of a role for Aβ and tau in the pathogenesis of glaucoma having found significantly decreased levels of Aβ and significantly increased levels of tau in the vitreous fluid from patients with these disorders in comparison with the levels in a control group (Yoneda et al., 2005). Their findings suggested that the neurodegenerative processes in these ocular diseases might share, at least in part, a common mechanism with AD. Numerous studies, including postmortem studies, have demonstrated significantly reduced numbers of RGCs and axons as well as RNFL thinning in patients with AD compared with controls (Sadun et al., 1990, Kirby et al., 2010, Blanks et al., 1989, Blanks et al., 1996, Danesh-Meyer et al., 2006). These are the earliest and key neurodegenerative findings in glaucoma (Quigley et al., 1992, Guo et al., 2010). It was demonstrated that a significant correlation between the RNFL thinning detected by optical coherence tomography and impaired RGC function, as indicated by pattern-reversal electroretinogram measurements in both glaucoma and AD (Parisi et al., 2003). Its intriguing that in AD, the cup:disc ratio has been found to be increased in comparison to controls (Lu et al., 2010, Danesh-Meyer et al., 2006). There is also further evidence to suggest that optic disc cupping and decreased disc rim area in AD is correlated with severity and duration of the disease (Tsai et al., 1991). Glaucoma and AD also show similarities in 'transmission' of neurodegenerative changes. A number of studies have shown that in both diseases, neuronal degeneration can be 'transmitted' from affected neurones to healthy neurones through connecting synapses, a phenomenon known as trans-synaptic degeneration (Yücel et al., 2008).

Neuroimaging

With regards to structural neuroimaging of patients with AD, atrophy of the medial temporal lobe, especially the hippocampus and the parahippocampal gyrus is regarded to be an important structural biomarker of AD in predicting the conversion from MCI