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Brain changes in glaucoma

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ABSTRACT. *There is evidence that glaucomatous damage extends from retinal ganglion cells to vision centers in the brain. In the lateral geniculate nucleus (LGN), the major relay center between the eye and the visual cortex, neurons should undergo degenerative and/or neurochemical changes in magno-, parvo-, and koniocellular pathways conveying motion, red-green, and blue-yellow information, respectively. Furthermore, in both the LGN and visual cortex in glaucoma, changes in metabolic activity are observed. The study of brain changes in glaucoma may provide new insights into the pathobiology of glaucomatous damage and disease progression, and may stimulate new detection and therapeutic strategies to prevent blindness.* Eur J Ophthalmol 2003; 13: (Suppl3): S32-S35

KEY WORDS. *Secondary degeneration, Lateral geniculate nucleus, Magnocellular, Parvocellular, Koniocellular, Visual cortex.*

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INTRODUCTION

The vast majority of knowledge regarding the pathobiology of glaucoma derives from ocular studies. Retinal ganglion cells (RGCs) have been shown to die by apoptosis in glaucoma (1) and a number of mechanisms have been implicated (2). In addition to RGC death in glaucoma, there is recent evidence that glaucomatous damage extends to the three major visual pathways in the central nervous system (CNS). Ninety percent of RGCs project to the LGN, the major relay center between the eye and the visual cortex. Here, parallel central visual pathways are segregated into anatomically distinct layers: neurons in magnocellular layers and parvocellular layers convey motion and red-green information respectively, while koniocellular neurons intercalated between these layers convey blue-yellow information (3,4).

Central visual pathways in glaucoma

Evidence of cell death in the glaucomatous LGN has been recently reported (5, 6). There is significant loss of relay neurons specifically destined for the visual cortex in both magnocellular and parvocellular layers following moderate to severe optic nerve fiber loss (5). The transneuronal degeneration in the LGN following RGC loss in glaucoma is a well known phenomenon of neurodegenerative disorders such as Alzheimer's disease (7) and amyotrophic lateral sclerosis (8) in which injury spreads from diseased neurons to connected neurons.

In response to injury, neurons may alter their protein expression, metabolic activity and cell size, and these changes may promote survival or lead to neuron death. Altered expressions of a structural protein called neurofilament and of a presynaptic molecule

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called synaptophysin, are observed in both magno- and parvocellular neurons in the glaucomatous LGN (9). Relatively reduced metabolic activity detected with the mitochondrial enzyme cytochrome oxidase is also evident (9,10). Shrinkage of LGN neurons in the glaucomatous LGN is noted relatively early in the disease (6, 11) and prior to optic nerve fiber loss (11). The shrinkage of relay neurons in the LGN increases with increasing injury to RGC axons (Fig. 1). The linear relationship between neuron shrinkage and loss of RGC axons is apparent for both magnocellular and parvocellular LGN neurons (Fig. 2).

Koniocellular neurons of the LGN make up the third channel, a more recently discovered visual pathway conveying blue-ON information (3, 4). These neurons express a specific marker called calmodulin dependent kinase type II-α, a post-synaptic density protein (3). In the glaucomatous LGN, expression of this molecule is dramatically decreased in monkeys with ocular hypertension without significant RGC loss and also following mild, moderate and severe glaucomatous optic nerve damage (12). Thus, degenerative and/or neurochemical changes are present in all three visual pathways at early as well as late stages of disease.

Changes in the relay neurons projecting to the primary visual cortex predict changes at this level also. Indeed, visual cortex ocular dominance columns driven by the glaucomatous eye show relatively decreased metabolic activity, observed in cortical sublayers 4Cα, 4Cβ, (9,10) and cytochrome oxidase (CO) rich blobs in layers 2-3 (13). We have observed high contrast CO staining between ocular dominance columns driven by glaucoma and non-glaucoma eyes in cases of greater than 60% optic nerve fiber loss (12). This finding suggests that these cortical changes are related to RGC loss and not solely to elevated IOP induced activity changes (14).

Implications

The anatomy and physiology of the primate central visual system have striking similarities to the human visual system, and experimental glaucoma closely mimics human disease (15, 16). Quantitative assessment of the degenerative changes in the glaucomatous primate brain demonstrates that the major visual pathways are affected, and these findings are in keeping with visual dysfunctions related to magno-, parvo- and

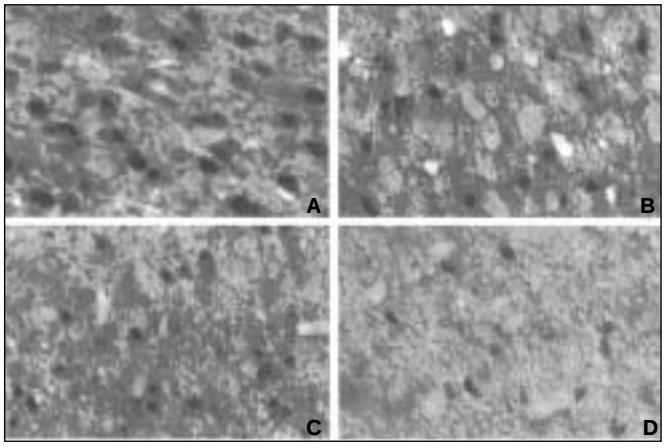

Fig. 1 - *Relay neurons of parvocellular LGN layer 4, compared to the normal control* (**A**), *show overall cell body shrinkage in glaucoma monkeys with 29%, 61%, and 100% optic nerve fiber loss* (**B,C** *and* **D**, *respectively) and this increases with increasing optic nerve fiber loss (Bar=10µm). (This figure has been reprinted from Yücel YH, Zhang Q, Weinreb RN, Kaufman PL, Gupta N. Atrophy of relay neurons in magno- and parvocellular layers in lateral geniculate nucleus in experimental glaucoma. Invest Ophthalmol Vis Sci 2001; 42: 3216-22. A copyright authorization has been obtained from the Association for Research in Vision and Ophthalmology.)*

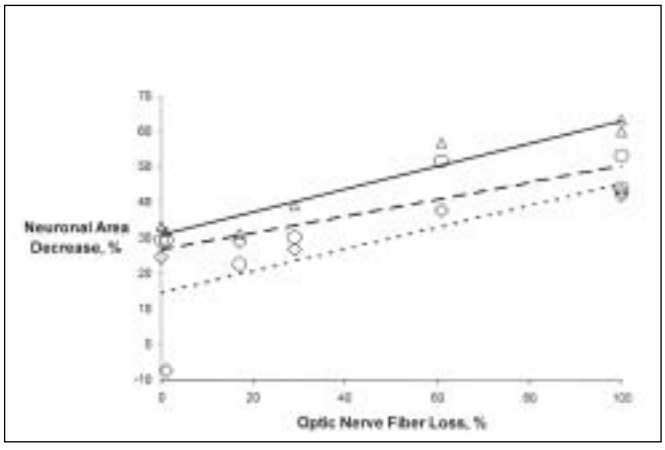

Fig. 2 - *Plot of neuronal area % decrease for magnocellular layer 1 and parvocellular layers 4 and 6 as a function of % optic nerve fiber loss. The linear regression lines are superimposed on the plots. Dotted, dashed and solid lines represent regression lines for layer 1, layer 4, and layer 6, respectively. Diamonds, circles and triangles correspond to the mean neuronal area % decrease for layer 1, layer 4, and layer 6, respectively. (This figure has been reprinted from Yücel YH, Zhang Q, Weinreb RN, Kaufman PL, Gupta N. Atrophy of relay neurons in magno- and parvocellular layers in lateral geniculate nucleus in experimental glaucoma. Invest Ophthalmol Vis Sci 2001; 42: 3216-22. A copyright authorization has been obtained from the Association for Research in Vision and Ophthalmology.)*

koniocellular pathways in patients with glaucoma (17).

Neural degeneration in magno- and parvocellular pathways in experimental glaucoma implicates motion and red-green visual deficits in the disease process. Furthermore, the close relationship observed between these degenerative findings and RGC loss suggests that tests of these visual modalities might be useful to assess disease progression (17). Observations of neurochemical changes in koniocellular neurons in the presence of ocular hypertension without significant RGC axon loss, suggest that elevated IOP may alter the CNS in early glaucoma. Blue-ON deficits in patients with ocular hypertension support this notion (18,19). Further investigations of brain changes in early experimental glaucoma are needed to understand the impact of elevated IOP on the RGCs and their target neurons.

Functional tests used to detect vision loss in glaucoma are often interpreted in relation to the degree of optic nerve damage. Neurophysiological (20-22) and functional neuroimaging (23) may help to investigate neuron populations along the retino-geniculo-cortical pathway in glaucoma. Investigations of the extrageniculate-cortical visual pathways in glaucoma may help to characterize the impact of glaucomatous damage on processes such as circadian rhythms and eye movements (24).

Following glaucomatous RGC loss, the degenerating target neurons may be incapable of sustaining trophic support to the remaining RGCs, and this may increase RGC susceptibility to ongoing damage. In fact, a significant loss of RGCs is observed after lesions of the LGN (25) and visual cortex (26). Degenerative mechanisms in target neurons are largely unknown, however, oxidative damage in the LGN has been suggested (27). Understanding the molecular pathways implicated in neural degeneration in glaucoma may lead to neuroprotective strategies directed at RGCs and their targets. Studies of brain changes in experimental models, and a multidisciplinary approach to investigate possible CNS damage in glaucoma patients, may provide novel insights into the pathobiology of glaucoma.

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