Title:

Neurodegeneration in Glaucoma: Microstructural MRI Evidence Within and Beyond the Visual Pathway

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Abstract:

PURPOSE

To investigate structural and microstructural brain changes in glaucoma through multi-modal magnetic resonance imaging (MRI) examining primary, secondary, and higher-order visual brain regions, and their associations with glaucoma diagnosis, retinal nerve fibre layer (RNFL) thickness, ganglion cell layer (GCL) thickness, and/or intraocular pressure (IOP).

METHODS

From UK Biobank, we identified glaucoma cases (n =1,465) and tenfold age- and sex-matched controls (n=14,650). MRI modalities comprised T1-weighted structural, diffusion tensor imaging (DTI), and neurite orientation dispersion and density imaging (NODDI). Associations with glaucoma status and ophthalmic measures (RNFL, GCL, IOP) were assessed using regression models adjusted for age, sex, and Townsend Deprivation Index.

RESULTS

Glaucoma was associated with reduced grey matter volume in primary visual regions (lateral geniculate nucleus, optic chiasm, intracalcarine cortex, and occipital pole) and DTI/NODDI abnormalities in the posterior thalamic radiation (all $p<0.001$). Secondary regions showed atrophy (lateral occipital cortex, lingual gyrus, and occipital fusiform gyrus), and microstructural changes in the inferior fronto-occipital and inferior longitudinal fasciculus (all $p<0.001$). Higher-order regions were also affected, including the right putamen and paracingulate gyrus ($p<.05$). RNFL ($p<0.05$) and GCL ($p<0.01$) correlated linearly with most primary visual regions, while IOP showed no significant associations.

DISCUSSION

Glaucoma is associated with widespread neurodegeneration extending beyond the eye to primary, secondary, and higher-order brain regions. These changes correlate strongly with RNFL and GCL thinning but not IOP. Involvement of the occipital pole supports trans-synaptic degeneration as a key feature of glaucomatous neurodegeneration.