

Widespread brain changes in patients with advanced glaucoma

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Target audience

Researchers with interest in neurodegenerative diseases

Purpose

To assess in patients with advanced Primary Open Angle Glaucoma (POAG) brain changes within and beyond the visual system and test their clinical relevance. POAG is the most common type of glaucoma, which is an important cause of irreversible blindness worldwide. Recent studies of quantitative MRI, supported by histological evidence, suggest that in glaucoma the entire visual system is involved¹⁻⁶. However, it is less clear to date whether brain changes are limited to the visual system and translate into clinically relevant functional changes.

Methods

We performed in 13 patients with advanced POAG (age=51.7±6.6 years) without other ophthalmological and neurological disorders a multimodal MRI approach comprising conventional MRI, Diffusion Tensor Imaging (DTI) and resting functional MRI. Data were compared with those of 12 age-matched normal controls (NC). Brain MRIs were acquired using a 1.5T Philips Gyroscan (Philips Medical Systems, Best, The Netherlands). MRI data postprocessing was performed with tools from Oxford FMRIB Software Library (FSL v5.0, www.fmrib.ox.ac.uk/fsl/)⁷. We used Tract-Based Spatial Statistics (TBSS) for microstructural integrity of white matter (WM) tracts, a Voxel Based Morphometry-style analysis of grey matter (GM) density (FSL-VBM) and group independent-component analysis (MELODIC) followed by individual timecourse regression (Dual Regression) for analysis of functional connectivity (FC) at the level of resting state networks (RSNs). Nonparametric permutation testing across the whole brain using threshold-free cluster enhancement (TFCE) was used for all voxelwise analyses ($p < 0.005$ uncorrected, $k \geq 30$ voxels). Visual fields were recorded using the Humphrey Field Analyser (Carl Zeiss Meditec, Dublin, CA, USA) and visual field indices were derived such as the Mean Deviation (MD), which provides a degree of the generalized loss in the visual field, and the Pattern Standard Deviation (PSD), which is a summary measure of the average deviation of individual visual field sensitivity values from the normal slope after correcting for any overall sensitivity differences.

Results

In POAG, altered microstructural integrity (decreased Fractional Anisotropy, increased Axial or Radial Diffusivity) of WM tracts was found in comparison with NC not only along the entire visual pathway (optic tracts/chiasm, optic radiations, WM of lateral occipital cortex [LOC]) but also throughout the brain in nonvisual-related WM tracts (middle cerebellar peduncle, posterior limb of the internal capsule mapping on the corticospinal tract, anterior thalamic radiation, superior longitudinal fascicle) (Figure 1).

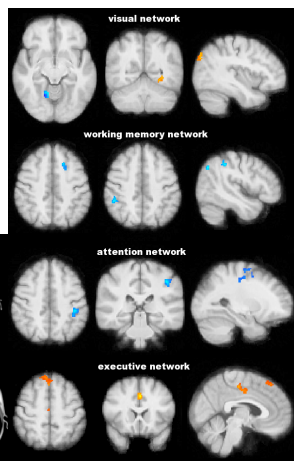


Figure 1 (left). TBSS analysis. Red-yellow show clusters where POAG patients have DTI abnormalities in comparison with NC. Green is the WM skeleton. Images are shown in radiological convention. See text for abbreviations.

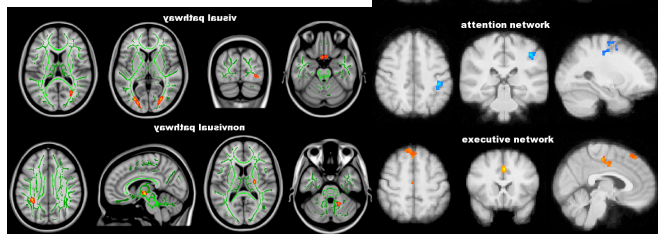


Figure 2 (right). FC analysis. Blue-light blue and red-yellow show the clusters where POAG patients have, respectively, lower and higher FC than NC. Images are shown in radiological convention. See text for abbreviations

Moreover, patients with POAG showed GM atrophy with respect to NC in both visual cortex (LOC and lingual gyrus) and other GM regions of the brain (frontoparietal cortex, hippocampi and cerebellar cortex). Patients with POAG showed also abnormalities in FC, independently of brain atrophy, in 5 of the 8 consistent (across all study subjects) RSNs. In particular, they had decreased FC in visual, working memory and attention networks, compared with NC (Figure 2). Conversely, increased FC was found in patients with POAG with respect to NC in visual and executive networks (Figure 2). Significant associations were found between visual field parameters (MD and PSD) in the worse eyes (right eye in 8 patients, left eye in 5 patients) of POAG and abnormalities in structure and FC in brain regions both within and outside visual system, independently of brain atrophy.

Discussion and Conclusion

In patients with advanced POAG structural and functional brain changes occur well beyond the visual system, and their topographic association with visual field points out their clinical relevance. Overall, these findings provide compelling evidence that POAG can be considered a vision disorder belonging to the group of neurodegenerative conditions, with a spreading of the neurodegenerative process throughout the brain.

References

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