Conventional MRI and magnetisation transfer imaging of the brain and optic pathway in primary open-angle glaucoma

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ABSTRACT. Neuropathological studies in experimental and human glaucoma have shown degenerative changes in the optic pathway. The purpose of the study was to evaluate, with conventional MRI and magnetisation transfer imaging, the brain and the optic pathway of patients with primary open-angle glaucoma (POAG). 26 patients, aged 67.4±8.6 years, and 26 control subjects were studied. The presence of white matter hyperintensities (WMH) was evaluated on fluid-attenuated inversion recovery images of the brain. The area of the optic nerves was assessed on coronal short tau inversion recovery images. Magnetisation transfer ratio (MTR) was measured in the chiasm and in the grey and white matter (CGM and CWM) of the calcarine fissure. More WMH were observed in patients (total 261, mean 10.8, standard deviation 12.7) than in control subjects (total 127, mean 4.7, standard deviation 5.7; $p<0.001$). The area (mm^2) of optic nerves (10.7±5.7) and the MTR (%) of the chiasm (53.7±8.4), the CWM (60.9±4.2) and the CGM (53.6±5.6) were all lower in patients than in control subjects (13.6±4.3, 62.1±6.2, 67.6±8.6 and 57.0±4.6, respectively; $p<0.05$). The area of optic nerves showed significant correlation with the MTR of the chiasm ($R=0.41$), the MTR of the CGM ($R=0.33$), the MTR of the CWM ($R=0.34$) and the cup to disc ratio ($R=-0.46$). POAG leads to optic nerve atrophy and degeneration of the optic pathway. The finding of an increase in the number of WMH suggests that cerebrovascular disease may play a role in the pathogenesis of POAG.

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Glaucoma is the second most common cause of blindness in the world, according to the World Health Organization. In most cases the disease is slowly progressive, causing no obvious symptoms until optic disc damage and visual loss are advanced. Primary open-angle glaucoma (POAG) is an acquired multifactorial syndrome, characterised by bilateral, very often symmetrical, progressive retinal ganglion cell death, leading to optic nerve head cupping, defects of the retinal nerve fibre layer and corresponding visual field defects [1]. Neuropathological studies, performed in experimental and human glaucoma, have demonstrated damage in the optic nerve head, the lateral geniculate nucleus and the visual cortex [2–7]. Kashiwagi et al [8], using conventional MRI, demonstrated atrophy of the retrobulbar optic nerve in patients with POAG and normal-tension glaucoma. A recent functional MRI (fMRI) study in POAG patients demonstrated alterations of the blood oxygen level-dependent (BOLD) signal in the visual cortex consistent with loss of visual function [9]. BOLD signal changes may not always represent direct evidence of cortical damage, and therefore fMRI signal alteration in the visual cortex does not necessarily confirm the presence of glaucomatous degeneration [9]. There have been no reports of imaging studies to evaluate the structural integrity of the optic pathway in patients with POAG. Structural changes in the optic pathway can be assessed using magnetisation transfer imaging (MTI), and this technique has proved to be useful in the study of acute optic neuritis and non-arteritic anterior ischaemic optic neuropathy [10, 11] but has never been used to study POAG.

Increased intraocular pressure (IOP) of >21 mmHg is considered to be a significant risk factor for POAG, but progressive loss of vision may occur despite the implementation of effective therapies to reduce IOP [12–14]. Vascular compromise has been proposed as an additional risk factor for POAG [12–14]. Small-vessel brain ischaemia has been described in patients with normal-tension glaucoma [15, 16]. In these patients, conventional MRI (cMRI) of the brain demonstrates increased numbers of white matter hyperintensities (WMH) [15, 16]. WMH are commonly observed in the elderly, and generally reflect covert vascular brain injury [11, 17, 18]. There have been no imaging studies evaluating the occurrence of WMH in patients with POAG.

The main goals of treatment of POAG are to arrest progress of the disease and to preserve visual function without causing complications from the therapeutic agents [1]. Because by the time visual disturbances are noticed death of >50% of ganglion cells has already taken place, the early detection of structural changes in the optic pathway and better understanding of the underlying causes of POAG may be useful in the application of more efficient therapies [19].

The purpose of this study of patients with POAG was to evaluate the optic pathway for structural changes,

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using MTI, and the brain for the presence of WMH, using cMRI.

Patients and methods

26 patients with bilateral high-tension POAG, 14 males and 12 females, aged 52–83 years (mean age 67.4, SD 8.6 years), and 26 age and sex-matched control subjects were enrolled in the study, having given informed consent. The diagnostic criteria for POAG were intraocular pressure $\geqslant$21 mmHg, glaucomatous optic disc and visual field abnormalities, and non-occludable anterior chamber angle. The disease duration was 1–15 years (mean $\pm$ SD 6.1 ± 3.8 years). Subjects were excluded from the study if they had demyelinating disease, autoimmune disease (vasculitis), history or clinical signs of cardiovascular disease, peripheral arterial disease, diabetes mellitus (fasting plasma glucose concentration $\geqslant$126 mg dl^{-1} or use of antidiabetic medications), hypertension (arterial blood pressure >140/90 mmHg or use of antihypertensive medications), other ophthalmic disease (optic neuropathy, etc), refractive error greater than +3.00 or greater than −6.00 dioptres, or a history of orbital or ocular trauma and optic nerve atrophy. All subjects underwent a complete ophthalmological examination including visual acuity, IOP (Goldmann tonometer), gonioscopy, fundoscopy with evaluation of the cup to disc (c/d) ratio, using the Discam imaging system (Marcher Enterprises Ltd, Hereford, UK), and assessment of visual fields (Humphrey, 30-2: mean deviation (MD), pattern standard deviation (PSD)).

All MRI examinations were performed on the same 1.5-tesla MR unit (Gyroscan ACS NT; Philips Medical Systems, Best, The Netherlands) using a head coil, a field of view of 24 cm and an acquisition matrix of 256×256 pixels. Subjects were asked to close their eyes and avoid any deliberate eye movements during image acquisition. The imaging protocol consisted of axial and coronal short tau inversion recovery (STIR)-weighted images (repetition time (TR), 2650 ms; echo time (TE), 90 ms; slice thickness, 3 mm; intersection gap, 0.3), axial turbo spin echo T_2 weighted images (TR, 3000 ms; TE, 90 ms; inversion time (TI), 180 ms; slice thickness, 6 mm; intersection gap, 0.6) and sagittal fluid-attenuated inversion recovery (FLAIR)-weighted images (TR, 6300 ms; TE, 90 ms; TI, 2150 ms; slice thickness, 6 mm; intersection gap, 0.6). To study the magnetisation transfer (MT) phenomenon, a three-dimensional gradient-echo sequence (TR, 32 ms; TE, 8 ms; flip angle, 6°; slice thickness, 2 mm; interslice gap, 0 mm) with and without the application of an MT binomial pre-pulse (1-2-1) applied on resonance was performed. Images of this sequence obtained before the application of the MT pre-pulse had a proton density contrast due to the short repetition time and the small flip angle. The MT sequence was performed in the axial plane (parallel to the intercommissural line) and in the coronal plane (perpendicular to the intercommissural line). Two radiologists, who were unaware of the clinical status of the patients and the control subjects, evaluated all MRI examinations in concert. The presence and the numbers of WMH were evaluated on sagittal FLAIR sequences (Figure 1). Area measurements were performed in the middle portion of the retrobulbar optic nerve (6–7 mm behind the optic nerve head) on coronal STIR images (Figure 2). Measurements were performed on the monitor screen using a computer-assisted calliper system. Magnetisation transfer ratio (MTR) of the chiasm and the grey and white matter (CGM and CWM) of the calcarine fissure were evaluated bilaterally using the region of interest (ROI) method (Figures 3 and 4). The ROIs were positioned on an image without MT and copy and pasted to the corresponding image with MT. The MTR was calculated as: $MTR = (SIo - SIm)/SIo \times 100$ (%), where SIm refers to the signal intensity from an image acquired with an MT pre-pulse and SIo to the signal intensity from the image acquired without an MT pre-pulse. Images with MT present a good grey–white matter contrast and white matter appears with lower signal intensity than grey matter. For each measurement ROIs were adjusted to avoid partial volume averaging with adjacent tissues. CGM and CWM measurements were obtained in Brodmann area 17. To identify Brodmann area 17, the interactive atlases included in the WFU Biological Parametric Mapping Toolbox were used [20].

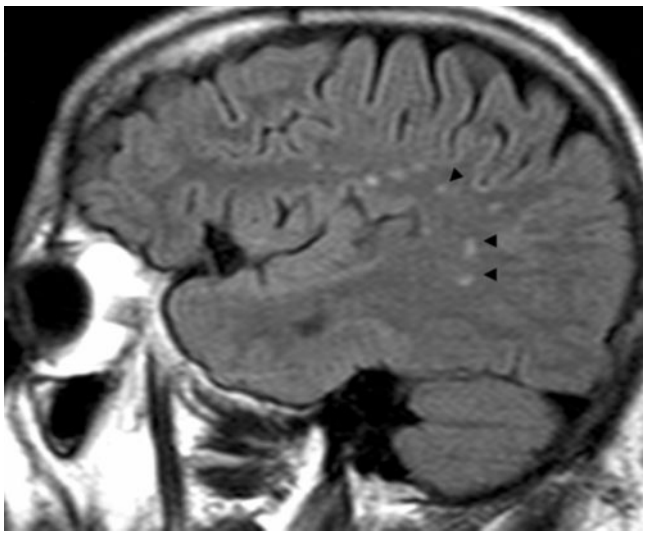

Figure 1. A 64-year-old man with primary open-angle glaucoma: fluid-attenuated inversion recovery (repetition time, 6300 ms; echo time, 90 ms; inversion time, 2150 ms) sagittal MR image of the brain shows areas of white matter hyperintensities (black arrowheads).

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) base 14 for windows. The normality of distribution of the parameters was assessed by the Kolmogorov–Smirnov test. The unpaired two-tailed Student's *t*-test was used to study differences between patients and control subjects in the c/d ratio, the area of the optic nerve, the MTR of the chiasm, the MTR of CWM and the MTR of CGM. The Mann–Whitney *U*-test was used to study differences between patients and control subjects in the numbers of WMH. The Pearson correlation coefficient was used to study the relationship between MTR and the optic nerve area. A p value of <0.05 was considered statistically significant.

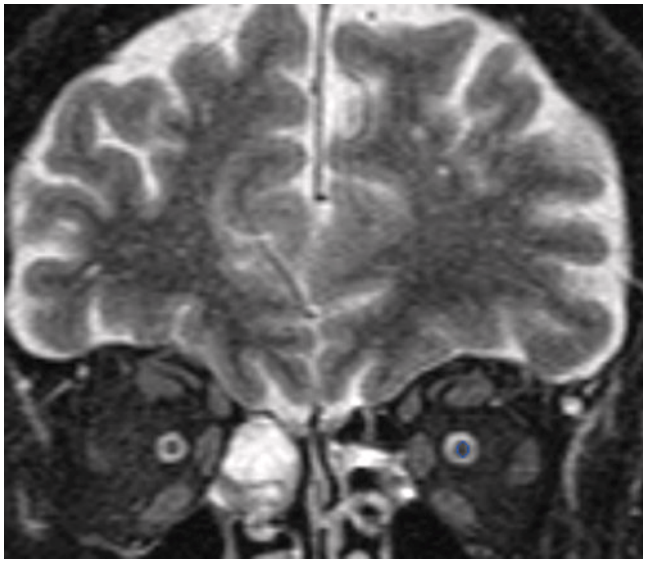

Figure 2. A 50-year-old man with primary open-angle glaucoma and atrophy of the optic nerves: short tau inversion recovery (repetition time, 3000 ms; echo time, 90 ms; inversion time, 180 ms) coronal brain MR image shows a region of interest positioned in the left optic nerve.

Results

Demographic information on the glaucoma patients and the healthy control subjects is presented in Table 1. Age, sex and spherical correction were not significantly different between the two groups. Because there was no significant difference in the disease duration between the left and right sides, the data on the c/d ratio, the area of the optic nerve and the MTR of CWM and CGM from both sides were combined. The mean c/d ratio was significantly higher in the patients (0.57 ± 0.18) than in the control subjects (0.27 ± 0.04; $p<0.05$). The area (mm^2) of the optic nerve was significantly less in patients (10.7 ± 5.7) than in control subjects (13.6 ± 4.3; $p<0.05$). The MTR (%) of the chiasm (53.7 ± 8.4), the CWM (60.9 ± 4.2) and the CGM (53.6 ± 5.6) were lower in the patients than in the control subjects (62.1 ± 6.2, 67.6 ± 8.6, 57.0 ± 4.6, respectively; $p<0.05$). Visual inspection of the occipital lobes did not demonstrate any atrophy. The area of the optic nerve showed a significant positive correlation with the MTR of the chiasm ($R=0.41$), the MTR of the CGM ($R=0.33$) and the MTR of the CWM ($R=0.34$), and a significant negative correlation with the c/d ratio ($R=0.46$, $p<0.05$). A greater number of WMH was observed in patients (total 261, mean 10.8 ± 12.7) than in control subjects (total 127, mean 4.7 ± 5.7; $p<0.001$).

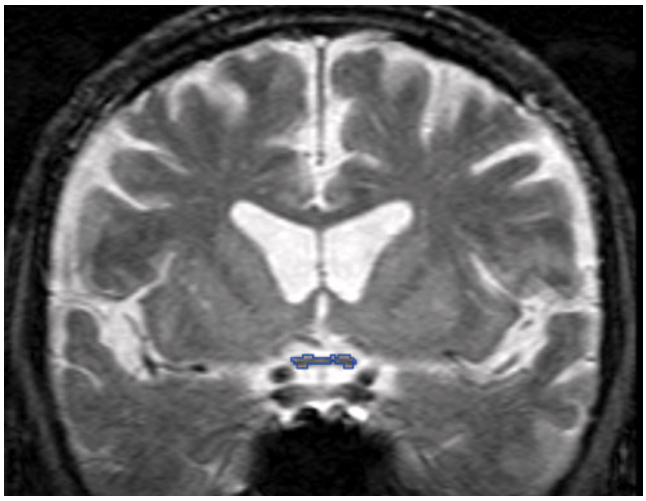

Figure 3. A 75-year-old woman with primary open-angle glaucoma: coronal three-dimensional gradient-echo scans (repetition time, 32 ms; echo time, 8 ms; flip angle, 6°) with the application of magnetisation transfer pre-pulse shows a region of interest on the optic chiasm.

Discussion

In this study, patients with POAG and control subjects were evaluated using cMRI and MTI. The major findings in POAG patients were optic nerve atrophy, degeneration of the chiasm, optic cortex and subcortical white matter, and microvascular brain injury.

The optic nerve is a tract of white matter formed of over one million unmyelinated axons originating from the retinal ganglion cells. The intraocular optic nerve is divided into three parts, the pre-laminar, the laminar and the retrolaminar. The pre-laminar part represents the ophthalmoscopically evaluated optic disc, which is oval shaped with a temporally located axon-deprived depression named the cup. The retinal ganglion cell axons become myelinated in the retrolaminar part of the optic nerve [21]. POAG is characterised by selective retinal ganglion cell loss linked to apoptotic cell death [22]. Retinal ganglion cell death and Wallerian degeneration of the corresponding axons is followed by further extension of the degenerative process through synaptic connections along the optic pathway up to the visual cortex [6]. This process of neuronal death extension among communicating neurons, which is common in neurodegenerative disorders, is named transynaptic degeneration [6]. Axonal degeneration of the optic nerve head leads to cup enlargement, resulting in the increased c/d ratio that is assessed ophthalmoscopically [12]. Axonal degeneration may also explain the decreased cross-sectional area of the optic nerve demonstrated by ultrasound and MRI in patients with POAG [8, 23]. In this study atrophy of the middle portion of the optic nerve was observed, with a significant negative correlation between the area of the optic nerve and the c/d ratio, probably related to the common process of axonal degeneration that causes optic nerve atrophy and increase in the cup area.

Experimental studies in glaucoma have demonstrated damage to retinal ganglion cells, the lateral geniculate nucleus of the thalamus and the primary visual cortex [3–5, 24–26]. Neuronal degeneration of the optic nerve, the lateral geniculate nucleus and the visual cortex has also been observed in post-mortem studies of patients with glaucoma [6, 7]. Alterations in the neuronal activity of the visual cortex, consistent with loss of visual function, have been demonstrated by fMRI in patients with POAG [9]. In the present study, a decrease in the MTR of the optic chiasm and in the grey and white matter of the calcarine fissure was found. MTI, which provides tissue contrast dependent on the presence of

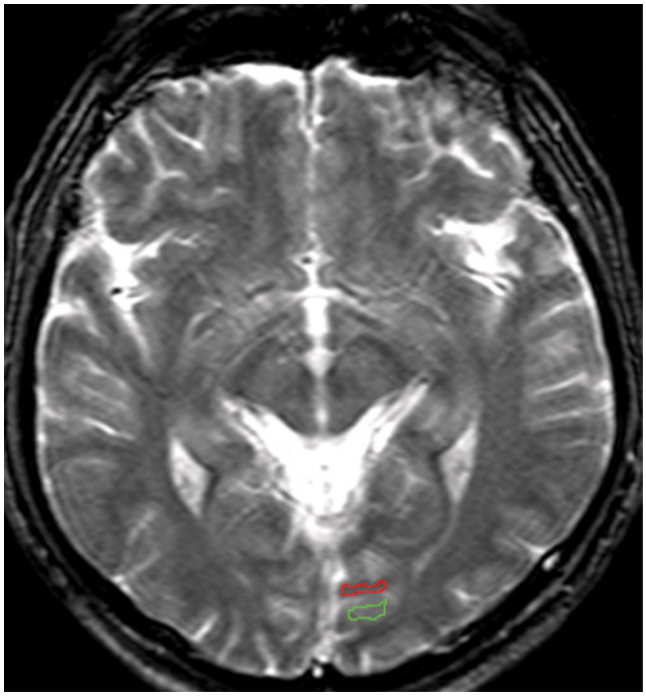

Figure 4. A 60-year-old woman with primary open-angle glaucoma: axial three-dimensional gradient-echo scans (repetition time, 32 ms; echo time, 8 ms; flip angle, 6°) with the application of magnetisation transfer pre-pulse shows regions of interest in the cortex (green) and white matter (red) of the calcarine fissure in the left occipital lobe.

macromolecules (*e.g.* myelin), has proved superior to cMRI in detecting and quantifying subtle brain changes [27–29]. MTR quantifies the phenomenon of magnetisation transfer, and reduction in this parameter is thought to represent axonal and myelin loss [27–29]. Axonal degeneration and demyelination of the optic pathway and the visual cortex might account for the low MTR in the study patients. Visual inspection did not reveal atrophy of the visual cortex in this study. Nevertheless, further dedicated volumetric studies are required to definitely address this question.

Another finding of this study was a significant positive correlation between the optic nerve area and the MTR of the optic pathway, indicating an association between the degree of optic nerve atrophy and the extent of degenerative changes in the visual cortex. Experimental studies in primate glaucoma have demonstrated that increased IOP induces injury of the lateral geniculate nucleus neurons, without detectable optic nerve atrophy [26]. From this study it is not possible to assess whether the optic nerve injury precedes or follows damage to more central parts of the optic pathway, probably because the study subjects were patients with disease of long duration. Further studies in early POAG would be useful to identify which part of the optic tract is affected first by the degenerative process.

There is controversy concerning the pathogenesis of the degenerative changes in the optic nerve of patients with glaucoma. According to some authors, optic nerve atrophy may result from the mechanical effects of raised IOP on axon bundles, while others maintain that it occurs in response to a disturbance of the vascular flow in the optic nerve [30–33]. Glaucomatous increased the c/d ratio and optic nerve atrophy may occur in the presence of both high-tension and normal-tension glaucoma [8, 34]. Although current therapies for glaucoma focus on lowering and maintaining a target IOP, its reduction is not always sufficient to prevent further optic pathway changes and vision loss [35, 36]. MRI studies of the brain in normal-tension glaucoma demonstrated higher numbers of WMH in patients than in control subjects [15, 16]. Thus, in normal-tension glaucoma, circulatory insufficiency in the brain appears to be related to the pathogenesis of glaucomatous optic neuropathy. More precisely, retinal ganglion cells are sensitive to ischaemia, and circulatory insufficiency within the territory of the short posterior ciliary arteries may lead to neuronal death associated with axonal disruption [11]. Circulatory insufficiency, expressed as decreased cerebrovascular blood velocity and vasoreactivity, has been demonstrated by transcranial Doppler in patients with POAG [37]. WMH have been associated with increasing age; nevertheless, after correcting for age, the number of WMH was associated with the extent of vascular risk [38]. In this study significantly higher numbers of WMH were found in the patients with POAG than in age-matched control subjects, suggesting that cerebrovascular disease plays a role in its pathogenesis.

In conclusion, POAG leads to optic nerve atrophy and degeneration of the entire optic pathway. The finding of increased numbers of WMH in the brain of patients with POAG suggests that hypoperfusion due to microangiopathy may play a pathogenetic role.

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Table 1. Mean values with standard deviations of the age, visual acuity and sex distribution in the group of patients with primary open-angle glaucoma and the group of control subjects

	Patients (n=26)	Control subjects (n=26)
Age (years)	67.4±8.6	68.1±8.3
Visual acuity	0.83±0.2	0.82±0.16
Sex	Male-to-female ratio, 14:12	Male-to-female ratio, 14:12

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