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Magnetic resonance in studies of glaucoma

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Summary

Glaucoma is the second leading cause of blindness. It affects retinal ganglion cells and the optic nerve. However, there is emerging evidence that glaucoma also affects other components of the visual pathway and visual cortex. There is a need to employ new methods of *in vivo* brain evaluation to characterize these changes. Magnetic resonance (MR) techniques are well suited for this purpose. We review data on the MR evaluation of the visual pathway and the use of MR techniques in the study of glaucoma, both in humans and in animal models. These studies demonstrated decreases in optic nerve diameter, localized white matter loss and decrease in visual cortex density. Studies on rats employing manganese-enhanced MRI showed that axonal transport in the optic nerve is affected. Diffusion tensor MRI revealed signs of degeneration of the optic pathway. Functional MRI showed decreased response of the visual cortex after stimulation of the glaucomatous eye. Magnetic resonance spectroscopy demonstrated changes in metabolite levels in the visual cortex in a rat model of glaucoma, although not in glaucoma patients. Further applications of MR techniques in studies of glaucomatous brains are indicated.

key words: glaucoma • retinal ganglion cells • neuroprotection • neurodegeneration • MRI • NMR

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BACKGROUND

Glaucoma is the second leading cause of blindness worldwide [1]. Moreover, in contrast to cataract, which is the leading cause of blindness, blindness caused by glaucoma is irreversible. Since progression of the disease is prolonged and may remain unnoticed for many years, it has been referred to as a 'sneaky thief of sight'.

In fact, the term glaucoma describes a group of diseases with varying etiologies, which have 2 common clinical features [2]: glaucomatous pattern of visual field loss [3] and optic nerve neuropathy resulting in 'optic disc cupping' (increased cup/disc ratio) [4]. The disease is classified as 'primary' if there are no signs of ocular pathology that elevate intraocular pressure (IOP) above the normal range (role of the elevated IOP in glaucoma is described in the next paragraph), or 'secondary' if such a pathology is identified. Secondary glaucomas are further subdivided according to the type of the primary pathology (eg, uveitic, neovascular, traumatic, pseudoexfoliation glaucomas) [5]. There are also developmental glaucomas. Another subdivision of glaucoma depends on whether the drainage angle is open (open angle glaucoma) or closed (closed angle glaucoma) [6]. The most frequent type is 'primary open angle glaucoma' (POAG).

Formerly the definition of human glaucoma included elevation of IOP over the upper limit of the normal range (most frequently >21 mmHg). However, many individuals with elevated IOP will never develop glaucoma (this apparently benign condition is termed 'intraocular hypertension'), and quite a few people suffer from glaucoma while measurements of their IOP never exceed 21 mmHg (this condition is called 'normal tension glaucoma', NTG). Diagnosis of elevated IOP is therefore neither sufficient nor necessary to diagnose glaucoma; however, it is still regarded as a major risk factor for this disease. Elevated IOP might affect axonal transport, retrograde as well as anterograde, within the optic nerve [7,8]. This disturbs delivery of neurotrophic factors such as BDNF and its receptor, TrkB, which may be required for survival of retinal ganglion cells (RGC) [9,10].

An interesting hypothesis has been proposed according to which the etiopathologic factor is not the high IOP but the difference between IOP and intracranial pressure (ICP) [11]. The optic nerve is exposed to considerable forces acting across the *lamina cribrosa*. In a normal eye the lamina, which is 450 μm thick, is exposed to a pressure gradient of 4 mmHg, which is one of the highest pressure gradients that any nerve in the body is constantly exposed to [11]. Moreover, some studies have shown that in patients with glaucoma ICP is lower [11], whereas the *lamina cribrosa* is thinner [12], which means that their optic nerve is exposed to a higher damaging pressure [13]. This mechanism may explain the phenomenon of normal tension glaucoma. In animal experiments, Yablonski et al. [14] (observations published only in abstract form) found that chronic lowering of intracranial pressure led to glaucomatous damage of the optic nerve, and that simultaneous lowering of IOP prevented this damage.

In the human retina, glaucoma mainly affects the RGC layer, and selective RGC death is regarded as the hallmark of

glaucoma [15–17]. There are several proposed mechanisms of this selective cell death, including excitotoxicity [18], nitric oxide toxicity [19], oxidative stress [20,21] and trophic factors deficiency [22].

Although glaucoma is commonly considered as a retinal disease, there is substantial evidence that not only RGC and the optic nerve, but also upstream components of the visual pathway and visual cortex are affected [23]. Detailed information on how different components of the visual pathway are affected in glaucoma can be obtained with modern imaging techniques, in particular magnetic resonance imaging (MRI) and spectroscopy (MRS). Advances in visualizing visual pathways in the context of glaucoma were thoroughly reviewed by Garaci et al. [24]. Here, we focus on novel results concerning use of MR techniques in the field of glaucoma research.

MAGNETIC RESONANCE IMAGING (MRI) IN STUDIES OF GLAUCOMA

MRI makes it possible to visualize the bony structures of the skull including orbit, orbital apex, optic canal, as well as intraorbital masses, oculomotor muscles and retrobulbar adipose tissue. Moreover, the bulb of the eye, the lens inside it, optic nerve, sheath, optic chiasm, tracts and radiations can be visualized [25]. While the optic nerve and optic chiasm can be seen quite easily, other parts of the visual pathway may be more difficult to distinguish on MR images and may require more advanced techniques, as discussed later. Generally the ability to see the structure on MR image is based on the difference in signal strength between them and the surrounding tissue, for example between nerves and cerebrospinal fluid or between white and gray matter.

The optic nerve is a white-matter tract, which in the intraorbital part is surrounded by adipose tissue. This fat is characterized by high signal intensity, which makes the optic nerve easily discernible on MR images. Glaucoma leads to loss of neurons, and its progression can be observed through measuring the diameter of the optic nerve. Thinning of the optic nerve visible on MR images was most pronounced 15 mm behind the bulb and showed correlation with retinal nerve fiber layer thickness measured using optic coherence tomography [26]. The other MRI study also showed that the optic nerve diameter was significantly smaller in glaucoma patients (2.25 mm) in comparison with the control group (2.47 mm) [27].

The optic chiasm is surrounded by cerebrospinal fluid in the chiasmatic cistern, which makes it highly visible. Changes in the optic chiasm in glaucoma reflect the decreased number of axons in the optic nerve. The optic chiasm was atrophic and its height was shorter in patients with glaucoma, especially when huge visual field defects were present [27,28]. Correlation between the height of the optic chiasm and visual field defects was even stronger than the correlation between vertical cup-disc (VC/D) ratio (which is the basic parameter for assessing the progression of glaucoma) and visual field defects [28].

Despite the relatively poor sensitivity and resolution of the technique and small thickness of the retina, it is also possible to investigate the retina and its neural connections with

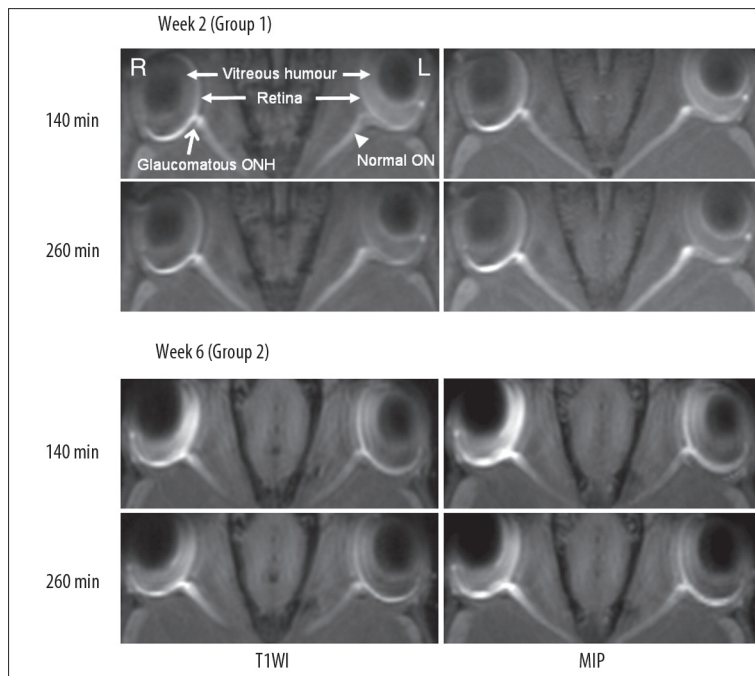


Figure 1. Typical T1-weighted images of the glaucoma model (1st column) and targeted maximum intensity projection of the optic nerves (2nd column) 140 min and 260 min after Mn²⁺ injection. Accumulation of Mn²⁺ ions at high concentrations was clearly observed at the glaucomatous optic nerve head (open arrow) compared to the normal optic nerve head in Week 2 (Group 1, top 2 rows) and Week 6 (Group 2, bottom 2 rows) animals. Significantly higher signal intensity in the vitreous humour of the glaucomatous eye was also found at 6 weeks after 1st laser treatment. Reprinted from Chan et al. [33]. Copyright (2008), with permission from Elsevier.

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MRI (Figure 1). Such studies can be performed using manganese as the dedicated contrast agent; the technique is called MEMRI (manganese-enhanced MRI). Mn²⁺ ions are paramagnetic and sites of their accumulation can be visualized by MRI because they shorten the T₁ relaxation time of the surrounding water protons, resulting in positive enhancement of the MR signal. Manganese ions, which behave as analogues of calcium ions, enter intraneuronal space by 2 mechanisms – through calcium voltage-gated channels during activation of neuronal cell and by specific metal ion transporters without concomitant electrical activity. Moreover, they are transported down axons via microtubule-based fast axonal transport and are able to cross synaptic clefts [29]. In rats, Mn²⁺ injected intraocularly were taken up by RGCs and transported along microtubules in the optic nerve, and further through chiasmata to the contralateral optic tract, the dorsal and ventral lateral geniculate nucleus, the superior colliculus and its brachium, the olivary pretectal nucleus, the nucleus of the optic tract, and the suprachiasmatic nucleus [30]. When MnCl₂ was administered systemically during a visual task, it acted as a functional biomarker of intraretinal ion regulation [31]. Moreover, thickness of the retina layers measured with high-resolution MEMRI technique was also used to assess changes in glaucomatous eyes in animal models [32]. One study showed accumulation of Mn²⁺ ions in the vitreous, retina and optic nerve head in a glaucomatous eye of a rat after intravitreal injection (Figure 1) [33]. Concentration of Mn²⁺ ions was higher in the glaucomatous eye than in the control eye, which could have been a reflection of decreased number of RGC cells, reduction in axonal density of the optic nerve and blockage of axoplasmic transport along the optic nerve [34].

MnCl₂ is not approved for humans, but there is another manganese-based contrast agent that is already used in humans – Mangafodipir (sold under brand name Teslascan) contains Mn²⁺ ions chelated by fodipir and is mainly used as

a contrast agent in imaging of the liver and allows discrimination of tumors and healthy hepatic tissue [35]. Some recent studies also have shown that mangafodipir is useful as a contrast agent in imaging of retina and visual pathways in animal studies [36,37].

DIFFUSION MRI

Diffusion of water molecules in tissues does not proceed equally in all directions – usually movement in 1 direction is predominant. Studies of water diffusivity provide information on cellular integrity, especially the integrity and connectivity of the white matter. Conventional MRI provides little information on diffusivity; however, as diffusing protons move through intrinsic and extrinsic field gradients they lose transverse magnetization. This phenomenon is used to create diffusion maps [38]. There are 2 subtypes of diffusion MRI – diffusion-weighted MRI (DW MRI) and diffusion tensor MRI (DT MRI). DW MRI applies when the observed tissue is dominated by isotropic water movement, and DT MRI applies when the tissue is dominated by anisotropic water movement. One application of DT MRI is tracking the nerve fibers (so called tractography). This technique can be used to visualize *inter alia* optic tract [39].

Hui et al. [40], using DT MRI, showed that in a rat model of ocular hypertension induced by laser photocoagulation of the episcleral and limbal veins, DT MRI-derived parameters (ie, radial diffusivity and fractional anisotropy) were affected in the optic nerve. Radial diffusivity was increased and fractional anisotropy decreased, suggesting that axonal density was reduced by around 10% when compared to control rats. Moreover, the authors performed DT MRI at various time points after photocoagulation and showed that radial diffusivity was increasing and fractional anisotropy was decreasing over time. These results were confirmed by histological evaluation of the optic nerve. Garaci et al. [41] reported similar findings in patients with POAG. Mean

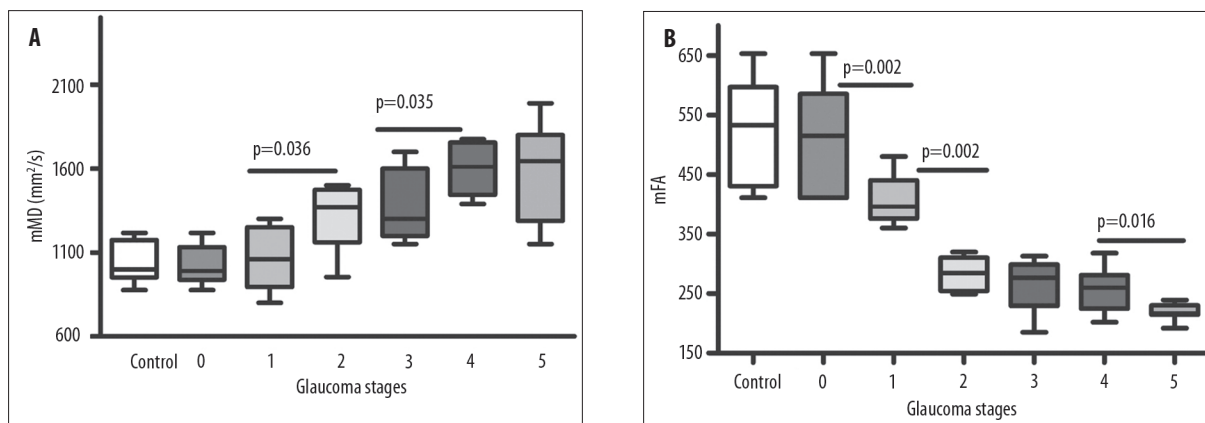


Figure 2. Graphs illustrate DT MR imaging–derived (A) mean MD (mMD) and (B) mean FA (mFA) values for optic nerves correlated with no glaucoma (control) and different stages of glaucoma. Median values (horizontal line inside box), ranges, and interquartile ranges are shown. Whiskers extending from each end of the boxes indicate minimal and maximal values. Reprinted from Garaci et al. [41]. Copyright (2009), with permission from Radiological Society of North America.

diffusivity was increased and correlated with the stage of glaucomatous optic neuropathy, while fractional anisotropy was decreased and also correlated with the stage of glaucoma (Figure 2).

FUNCTIONAL IMAGING

Functional MRI (fMRI) was a breakthrough in the imaging of the brain. This technique, known also as BOLD (blood oxygen level-dependent) imaging is based on observation of changes of the local cerebral hemodynamics accompanying changes in neural activity. Increased cerebral activity is followed by increase in blood flow, resulting in local lowering of deoxyhemoglobin to oxyhemoglobin ratio, because increased blood flow delivers more oxyhemoglobin than is needed. This allows visualizing brain activation locally using MR.

In particular, local changes in oxygenation of hemoglobin in the visual cortex corresponded with the visual stimulation of the eye, which made it possible to prepare a map of the cortical representation of the retina. Further study was performed to find the relationship between visual field loss in POAG (as measured with a standard automated perimetry) and visual cortex (V1) activation pattern evoked by a scotoma-mapping stimulus and measured with fMRI in unilateral glaucoma [42]. In that study it was found that altered patterns of neuronal activity in POAG were consistent with visual field deficits.

However, fMRI indices of altered visual cortex functional response in POAG may not have a simple and direct relation to the glaucomatous degeneration of the visual cortex. Recently, Qing et al. [43] used fMRI to investigate the impact of the glaucomatous neuropathy on the central normal visual field. These authors measured BOLD fMRI changes in the glaucomatous eyes with asymmetric peripheral visual field damage, but without changes in central vision. BOLD signals corresponding to the central vision field in the primary visual cortex were decreased in comparison to the signals from the non-glaucomatous eyes, despite the fact that there were no changes in patients' central visual fields.

MR SPECTROSCOPY

Magnetic resonance spectroscopy (MRS) is the technique that enables non-invasive assessment of levels of resonance-visible metabolites *in situ*. In this technique measurements of areas under metabolite resonances in a magnetic resonance spectrum are directly proportional to the concentration of these metabolites. Although MR spectra can be recorded for various nuclei (eg, phosphorus, fluorine, carbon ¹³C), in biomedical research proton (¹H) resonance spectra are of particular interest. The 3 most prominent resonance lines in the proton MR spectrum of the brain are those related to creatine and phosphocreatine (Cr, involved in cellular energy metabolism), choline compounds (Cho, associated with metabolism of cell membranes and involved in cholinergic transmission), and N-acetyl aspartate (NAA, considered to be the marker of neuronal integrity). Brain ¹H MRS data are frequently reported as the metabolite ratios (NAA/Cr, Cho/Cr, etc.). More advanced MRS paradigms allow calibration of resonance signals in terms of molar concentrations [44] and record up to 17 brain metabolites in animal experiments [45].

Although ¹H MRS has many potential clinical applications in the area of neurodegenerative diseases (eg, Parkinson's [46], Alzheimer's disease [38], and multiple sclerosis [47]), this technique has been rarely used in glaucoma studies. Chan et al. [48] recorded ¹H MR spectra in a rat model of ocular hypertension induced by photocoagulation of episcleral and limbal veins with an argon laser. Six weeks after initiation of intraocular hypertension, they found decreased Cho/Cr ratio in the visual cortex suggestive of a dysfunction in the cholinergic system of the visual pathway (Figure 3). However, Boucard et al. [49] could not detect statistically significant differences of NAA, Cr and Cho resonance signals in patients with POAG compared to non-glaucomatous controls. Different results from the animal and human studies may reflect a difference between the acute animal models (where quick degeneration is observed) and prolonged degeneration in humans subjects.

Ngumah et al. [50] also used MRS to analyze changes in lactate concentration in vitreous after induction of ocular

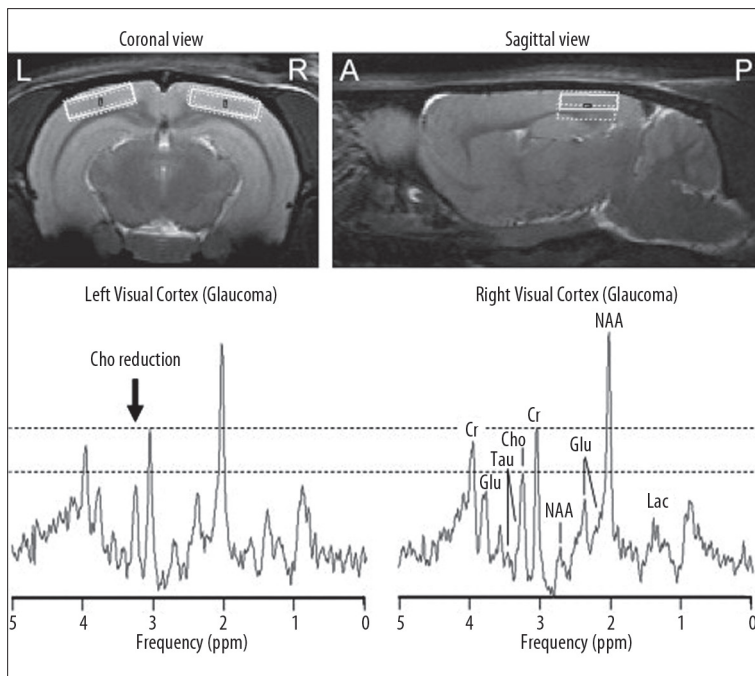


Figure 3. (Top row) Illustration of the localization of the $4 \times 4 \times 4$ mm³ voxels (solid-line boxes) in the glaucomatous (L) and control (R) rat visual cortex for ¹H MRS. (Bottom row) Averaged spectra for single voxel ¹H MRS on each side of the visual cortex. Note the apparently lower Cho signal (arrow) with respect to the Cr signal in the left glaucomatous visual cortex than in the right control visual cortex. (L: left; R: right; A: anterior; P: posterior.). Reprinted from Chan et al. [48]. Copyright (2009), with permission from Elsevier.

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hypertension in rabbits. They found a good correlation between rise in IOP and increased lactate signal. Performing localized MRS in the vitreous can be a useful tool in tracking pathological changes in experimental models of glaucoma and in human disease.

CONCLUSIONS

Glaucoma is a neurodegenerative disease that affects structure and functioning of the retina and optic nerve, and has an impact on morphology of chiasms and optic radiation. The function of the visual cortex is also affected, as revealed by fMRI. Changes in the optic nerve and visual cortex correlate with the progression of glaucoma. MR techniques seem to be useful tools for characterization of glaucoma-related changes in the visual pathway both in laboratory animals and in humans, and may prove useful as tools for monitoring the progression of glaucoma and assessing the efficacy of novel treatment strategies.

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