

Gd-DTPA-enhanced MRI Revealed Leakage at Aqueous-Vitreous Interface upon Ocular Hypertension

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INTRODUCTION: Glaucoma is a neurodegenerative disease of the visual system characterized by an increase in intraocular pressure (IOP). While this elevated pressure is believed to arise due to an increased resistance to the outflow of aqueous humour (1), their impacts to the etiology and pathogenesis of the disease are not fully understood. In this study, contrast-enhanced MRI (CE-MRI) was employed to monitor the ocular transport in an experimental model of chronic glaucoma.

MATERIALS AND METHODS:

Animal Preparation: Sprague-Dawley rats (250-280 g, N=11) were induced for ocular hypertension unilaterally in the right eye by photocoagulating the episcleral and limbal veins on the surface of the eyeball using an argon laser. This produced a consistent IOP elevation by 1.6 times above normal level up to a 12-week experimental period (2). CE-MRI was performed at Day 5 (Group 1, n=5) and Week 8 (Group 2, n=6) after laser treatment.

MRI Protocols: All MRI measurements were acquired utilizing a 7 T Bruker scanner. Under inhaled isoflurane anaesthesia (3% induction and 1.5% maintenance), animals were kept warm under circulating water at 37°C and were imaged using a receive-only surface coil. 2D T1-weighted RARE sequence was acquired before and at 10 to 80 minutes after intraperitoneal injection of an MRI contrast agent, Gd-DTPA (Magnevist) at 3 mmol/kg, with TR/TE = 320/8.9 ms, RARE factor = 4 and NEX = 26, FOV = 3.2 x 3.2 cm², voxel resolution = 82.3 x 82.3 μm² and slice thickness = 1 mm. Throughout the experiments, the left eye served as a control.

Data Analysis: In the 2D slice that centrally cut through the eyeball and optic nerve head, regions of interest (ROIs) were drawn manually on the whole anterior chamber, and on the vitreous body covering a distance of 3.5 mm on each side from the optic nerve head using ImageJ v1.38x (Wayne Rasband, NIH, USA). Each value was calibrated to the nearby saline phantom. A quantitative measure of the Gd-DTPA entry was obtained from the enhancement in the MR signal intensity defined as $E = |S(t) - S_0|/S_0$, where $S(t)$ is the calibrated signal intensity of the ROIs, and S_0 is the T1-weighted signal intensity before MR tracer injection. Differences between mean values of the ROIs on both sides were compared using two-tailed paired t-tests, and the mean values along the time course were compared using ANOVA. Results were considered to be significantly different when $p < 0.05$.

RESULTS AND DISCUSSION: The patterns of T1W signal enhancements in the control eye generally followed as previously described (3,4). Nevertheless, the vitreous body in the glaucomatous eye enhanced progressively from 10 minutes post-administration in both groups after glaucoma induction (Figs. 2 and 3), whereas no apparent signal increase was observed in the vitreous body in the control eyes. Further, there was an earlier Gd-DTPA transport into the anterior chamber in the majority of glaucomatous eyes (7/11). Qualitative inspection of the MR images suggested that Gd-DTPA leaked at the aqueous-vitreous interface and diffused into the anterior vitreous body of the glaucomatous eyes in all rats (Fig. 2), possibly due to increased permeability of blood-aqueous or aqueous-vitreous barrier. These CE-MRI findings may explain the sources of changing biochemical compositions in the glaucomatous chamber components (5-7), which may implicate the cascades of neurodegenerative processes in the retina and the optic nerve.

CONCLUSIONS: Given that aqueous-vitreous barrier and blood-retinal barrier are impermeable to Gd-DTPA in the normal intact eye (3,4), our findings of the early Gd-DTPA signal enhancements in the anterior vitreous body than the preretinal vitreous provided a noninvasive marker for the disease. Importantly, this approach could have direct clinical applications as Gd-DTPA is FDA approved and it can be readily translated to humans.

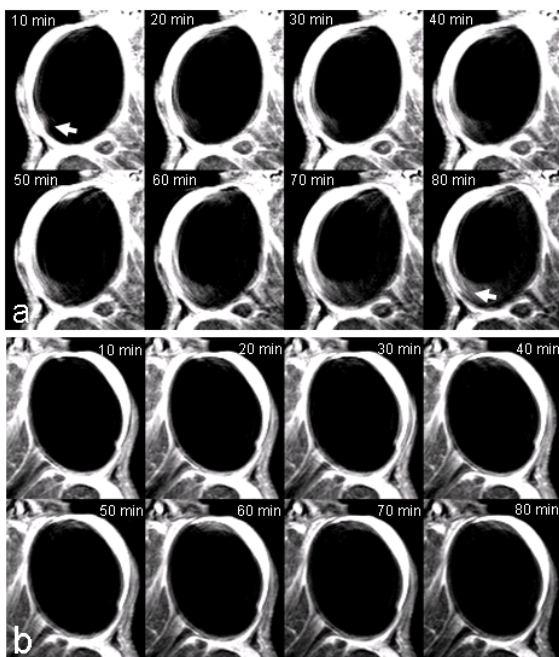


Fig 2: Windowed and zoomed serial T1WIs of the Week 8 (Group 2) glaucomatous (a) and control (b) eyeballs 10 to 80 minutes following systemic Gd-DTPA administration. Different extents of leakiness from the aqueous-vitreous interface (arrows) into the vitreous body were visible in the glaucomatous eye but not the control eye as time went by.

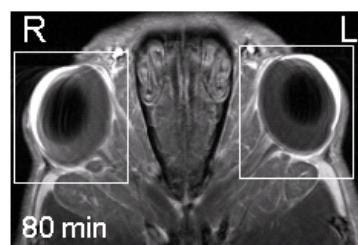


Fig 1: Typical T1W image of the glaucomatous (R) and control (L) eyes 80 minutes after Gd-DTPA administration. Rectangles represent the regions of interest for the serial images in Figure 2.

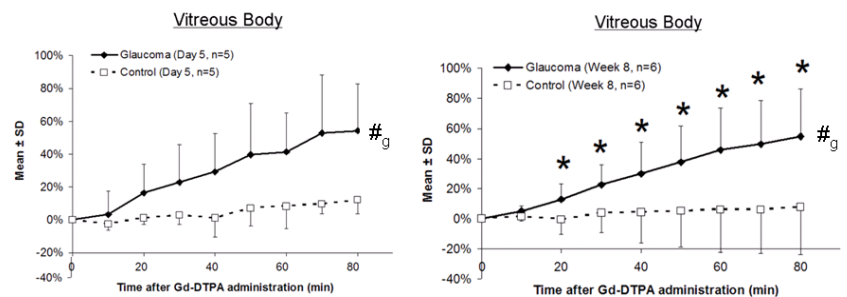


Fig 3: Time course of T1W signal enhancement of the vitreous body of both eyes before and after 10-80 minutes following Gd-DTPA administration at Day 5 (Left) and Week 8 (Right) after induction of ocular hypertension. The vitreous body did not enhance in the control eye, yet there was a progressive increase in signal intensity in the vitreous body of the glaucomatous eye (ANOVA across timeline in glaucomatous (g) and control (c) eyes with $\#p < 0.01$; Student's paired t-tests: * $p < 0.05$).

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