# MRI biomarkers capable of detecting effects of an experimental pharmacologic therapy for idiopathic Normal Pressure Hydrocephalus

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***Introduction*** Normal Pressure Hydrocephalus (NPH) is an idiopathic neurologic disorder associated with ventricular enlargement in the absence of elevated cerebrospinal fluid (CSF) pressure[1]. NPH is associated with cognitive decline, gait disturbance and urinary incontinence[2]. There are no proven pharmacologic treatments for NPH. Acetazolamide (ACZ) is carbonic anhydrase inhibitor known to reduce CSF production and interstitial edema. We hypothesized that a low dose of ACZ (125mg-250mg/day) would reduce CSF production and brain interstitial fluid in NPH.

Reliable quantitative markers are needed to assess the effects of experimental therapeutic approaches and screen patients before costly clinical trials are undertaken. Our task was to provide biomarkers capable of detecting whether ACZ affected white matter (WM) abnormalities, ventricular volume, CSF flow and cerebral blood flow.

***Methods*** Two clinically diagnosed NPH patients (72 old female and 87 years old male) received escalating doses of ACZ starting at 125mg ACZ PO daily and increased after 30 days to ACZ 250mg daily. The treatment lasted 90 days.

Both patient underwent clinical examinations MRI scans at baseline which were repeated after the treatment . T1, T2-FLAIR, Arterial Spin Label and Diffusion Weighted (DW-MRI) were performed on a 3T GE Signa EXCITE scanner. The parameters of the scans were chosen so that overall scanning time is around 40 mins. DW-MRI images were acquired using 33 isotropically distributed echo-planar diffusion weighted scans at b=1000 s/mm2 and one at b=0s/mm2, acquired at 72 1.8mm thick interleaved slices with no gap between slices and a 128 x 128 matrix size.

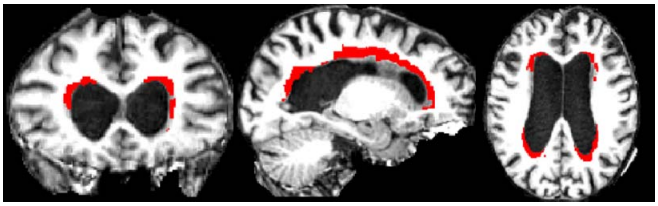

**Figure 1:** Regions of T1 hypo-intensities

T1 volumetric analysis with automatically detected T1 hypo-intensities was performed in *FreeSurfer*[3] and DW-MRI analysis was done by *FSL*[4]. The before and after scans were co-registered by *ANTS*[5]. We used conventional Diffusion Tensor metrics -mean diffusivity(MD) as it is, by definition, a suitable biomarker for interstitial brain water.

Percentage-wise voxel-based change in MD was defined as $(MD_{baseline}-MD_{after})/MD_{after}$. which was averaged over all the voxels in specific regions.

***Results*** ACZ brought significant reduction in WM abnormalities in both patients, with a maximum reduction of 38% in the total volume of automatically detected T1 hypointensities (19073mm$^3$ to 11782mm$^3$), T2-FLAIR hyperintensities decreased by as much as 35%, with most of the change near the poles of the lateral ventricles (see figure 1). Changes in ventricular volume and total cerebral blood flow were not detected.

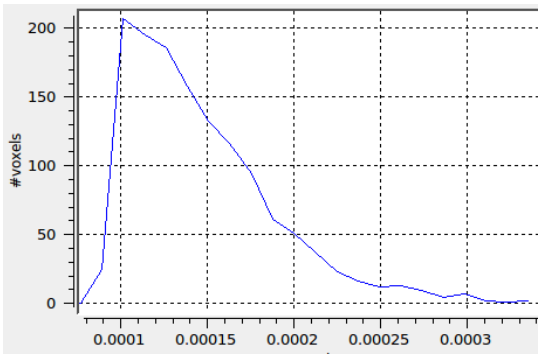


**Figure 2:** Voxel-wise difference in MD, within T1 hypointensities, between scans before and after the treatment. All the voxels exhibited decrease in MD after the treatment.

Further, by use of DW-MRI, we were able to show that the interstitial water in the remaining T1 hypointensities decreased even more than in the rest of the WM. Average percentage-wise decrease in MD over the remaining T1 hypointensities was 8.5% for one of the patients and 6.7% for the other. Even more importantly, all the voxels in the hypointensities showed a decrease, indicating a broad decrease, independent of co-registration artifacts see figure 2 and figure 3. Average diffusivity also decreased throughout the periventricular WM, the corpus callosum and thalamic WM.

To check for consistency, we performed an identical series of scans on a healthy volunteer. No WM abnormalities were detected and MD showed small, inconsistent change, with average difference <0.5%.

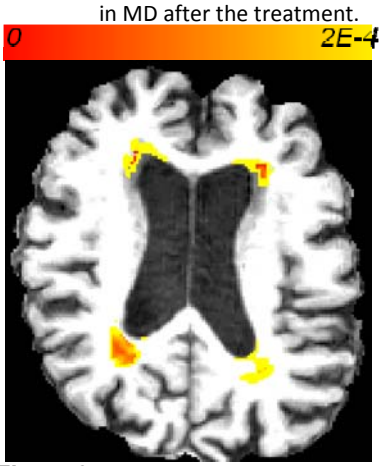


**Figure 3** The difference in MD, within T1 hypo-intensities, before and after the treatment.

***Conclusion*** By using a combination of DW-MRI, T1 and T2-FLAIR images, we were able to unequivocally detect that a low dose ACZ significantly reduced WM abnormalities and interstitial brain water in NPH patients. T2-FLAIR and T1 volumetrics showed consistent decrease in WM pathology.

By the use of DW-MRI we were able to detect changes within remaining areas of WM signal abnormalities which would otherwise have gone unnoticed. Net aqueductal flow was also reduced, consistent with ACZ reducing CSF production and/or increasing interstitial CSF clearance.

These results represent initial findings from an ongoing pilot study. Although this preliminary study was not designed to establish clinical efficacy, it is noteworthy that participants did experience symptomatic benefits. Our findings suggest that pharmacologic treatment of NPH is feasible and that properly selected quantitative MRI metrics can play important role in guiding further NPH drug development.

***References*** [1] Adams R et al. (1965). N Engl J Med 273: 117-126 [2] Relkin N *et al.* Neurosurgery 2005, 57: S4S16. [3] Fischl, B *et.al.* NeuroImage (2004) 23:S69-S84. [3] Smith S. *et.al.* NeuroImage, 2004, 23(S1):208-219. [4] Avants B *et.al.* Med Image Anal, 2008, 12, 26-41.