Altered axonal integrity of lower limb motor tracts in idiopathic normal pressure hydrocephalus: a DTI biomarker for differentiating lumbar-drainage responders from non-responders

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Introduction

Gait disturbance is the most common initial symptom in idiopathic normal pressure hydrocephalus (iNPH) [1,2]. The diagnostic workup of iNPH for shunt treatment may include invasive lumbar CSF drainage. However, only about 60% of the patients with iNPH show improvement after the treatment [3]. Recently, studies have indicated the early changes of white matter lesion in patients with iNPH using MR diffusion tensor imaging (DTI) [4-6]. As a result, we aimed to investigate the diffusional properties of the lower limb motor tracts in iNPH patients by using DTI and to determine whether these tensor parameters can be used as biomarkers to differentiate lumbar-drainage responders from non-responders in iNPH.

Materials and Methods

We prospectively enrolled 25 patients with iNPH and gait disturbance, and 17 age- and sex-matched controls for this study. All the subjects were imaged in a 1.5 T MR system (GE, Signa HDx) with an 8-channel head coil. In addition to the conventional MR imaging sequence, a spin-echo EPI sequence was used to target the diffusion information of white matters along 15 directions with b = 1000 s/mm^2, TR = 10000 ms, TE = 90 ms, matrix size = 128x128, slice thickness = 4 mm, and no gap. After data acquisition, DTIStudio (Johns Hopkins University, Baltimore, Maryland) was used to reconstruct the images and calculate the DTI-derived parameters (FA values, axial eigenvalues, and radial eigenvalues). A background noise level of 90 (MR units) was applied before calculation of the pixel-wise maps. The seed points for initiating the lower-limb corticospinal tracts (CST) were placed at 2 seed regions: the cerebral peduncle at the midbrain level and the primary motor cortex /precentral gyrus (Figure 1). Regions of interest (ROI) for corticospinal tracts were placed at pons, in order to avoid the displacement effect from the dilated lateral ventricle. To evaluate the shear effects from the hyperdynamic CSF on the corpus callosum, ROI were then placed at the genu, body and splenium of the corpus callosum, considering the different effects by the shear force in each region. All statistical analyses were performed with SPSS software (version 20, SPSS, Inc, Chicago, IL, USA). To compare groups with lumbar-drainage responders, non-responders and the control, the paired Student t test was applied. Receiver operating characteristic (ROC) curves were constructed to determine the optimum threshold for the axial eigenvalues to differentiate lumbar-drainage responders and non-responders.

Results

Tract-specific analysis of the lower-limb CST at pontine level showed that axial diffusivity (AD) were significantly increased (P = 0.043), whereas FA and radial diffusivity (RD) were not significantly altered, in patients with iNPH compared with the control (Figure 2). In corpus callosum, the distended body showed decreased FA and increased axial diffusivity. The non-responders revealed increased axial diffusivity than that of the responders ($P < 0.01$) (Figure 3). ROC analysis showed accuracy of 0.898 ($P< 0.001$), and a sensitivity of 100% and specificity of 100%, respectively, at a cutoff value of 0.0018.

Discussion

This study demonstrated the feasibility of using diffusion tensor metric measurements as biomarkers to provide the information of early changes at specific white matters in patients with iNPH. Gait disturbance in the patients is associated with altered axonal integrity in the corpus callosum and lower-limb motor tracts. The degree of axonal integrity changes is significantly increased in lumbar-drainage non-responders than the responders. In summary, our preliminary study indicated that DTI may potentially be useful in differentiating the responders from non-responders in the diagnostic workup of iNPH patients who might benefit from permanent ventriculo-peritoneal shunting treatment, thus providing a non-invasive method to improve the predictability of shunt responsiveness in INPH.

Reference

1. Koyama T, et al. Neurol Med Chir, 2012;52:68-74
2. Gallia GL, et al. Neurology, 2006;2:375-81
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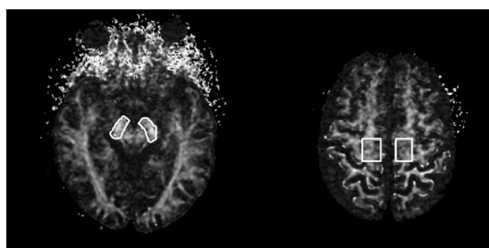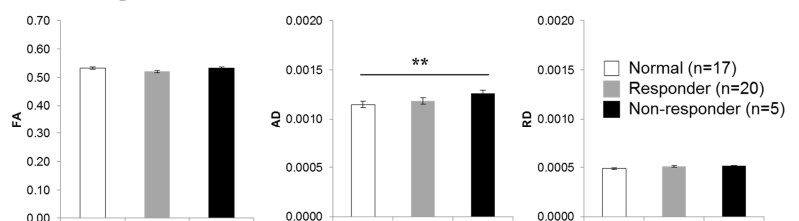Fig 2. DTI parameter changes in the lower-limb CST at pontine level. AD and RD values in mm^2/s (mean ± SD).

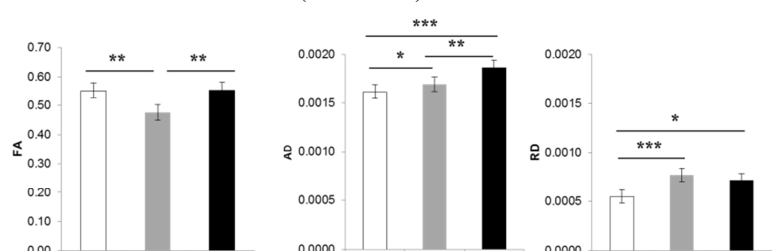Fig 1. Illustration of seed ROIs setting for the lower-limb corticospinal tracts in this study.

Fig 3. DTI parameter changes in the body of the corpus callosum. AD and RD values in mm^2/s (mean ± SD). Stars indicate different significance levels (*<0.05, **<0.01, ***<0.001)