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Diffusion tensor imaging of idiopathic normal-pressure hydrocephalus and the cerebrospinal fluid tap test

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ABSTRACT

We evaluated relationships between diffusion tensor imaging (DTI) findings and clinical profiles in idiopathic normal-pressure hydrocephalus (INPH) patients, along with differences in DTI parameters between cerebrospinal fluid tap test (CSFTT) responders and non-responders.

Fifty-four INPH patients constituted the final group for analysis. Fractional anisotropy (FA), axial diffusivity, radial diffusivity, and mean diffusivity were assessed using atlas-based tract-mapping methods on 20 different fiber tracts.

Uncorrected results revealed that CSFTT non-responders, when compared to responders, exhibited lower FA in the left anterior thalamic radiation (ATR), left cingulum–hippocampus (CgH), and left inferior fronto-occipital fasciculus (IFO) and higher axial diffusivity, radial diffusivity, and mean diffusivity in the left CgH and left inferior longitudinal fasciculus (ILF). FA values in the ATR (bilateral), corticospinal tract (right), IFO (bilateral), and ILF (bilateral) were negatively correlated with Unified Parkinson's Disease Rating Scale motor scores. In the right CgH, FA values showed significant positive correlations with Korean-Mini Mental State Examination scores and negative correlations with Clinical Dementia Rating Scale scores.

Our findings may suggest a possibility for considering microstructural changes of white matter in patients with ventriculomegaly as potential imaging markers for the prediction of CSFTT responders. Unique patterns of white matter microstructural changes, as measured using DTI, might underlie impairments in distinct symptom domains in patients with INPH.

1. Introduction

Idiopathic normal-pressure hydrocephalus (INPH) is an adult-onset syndrome of uncertain origin, with symptoms of gait disturbance, cognitive deterioration, and urinary dysfunction, involving nonobstructive enlargement of the cerebral ventricles along with normal cerebrospinal fluid (CSF) pressure at lumbar puncture [1]. Patients with INPH may present with varying combinations or degrees of each of these classic clinical symptoms. INPH is regarded as a potentially treatable syndrome by shunt surgery.

It has been suggested that the destruction of neural tracts associated with ventricular enlargement can precipitate the typical deficits of motor and cognitive function observed in INPH patients [1]. Disorders of white matter are generally viewed as the principal pathological features of INPH [2,3]. Diffusion tensor imaging (DTI) is sensitive to microstructural changes in white matter integrity not always detectable by routine magnetic resonance imaging (MRI) [4]. The most widely used DTI indices are fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD) [5]. DTI is an important tool for probing the effects of neurodegenerative disorders, including INPH [2,4,6].

The CSF tap test (CSFTT) has been known as a valuable tool for diagnosis in patients with INPH [7,8]. The CSFTT response has been regarded as an important mark for the prediction of shunt effectiveness in patients with INPH and a valuable characteristic for understanding INPH patients [7,8]. There may be relevant relationships between measures of white matter and CSFTT response heretofore unknown. One hypothesis is that certain microstructural changes of vulnerable connectivity in INPH may also affect CSFTT response. Analyzing DTI measures in various brain regions between CSFTT responders and non-responders might shed light on that issue.

To date, there have been a few investigations into specific relationships in INPH patients between DTI-based findings and clinical characteristics, but their results are inconsistent [3,4,9]. For example, while

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FA and MD values in the corticospinal tract (CST) correlated with poorer cognitive performance, as measured by the Mini-Mental State Examination (MMSE) [4], FA values within the CST did not correlate with the INPH Grading Scale (INPHGS) cognition score [9].

We broadly investigated 20 different fiber tracts (i.e., 9 tracts in each hemisphere and 2 inter-hemispheric tracts) utilizing DTI and automated atlas-based tract-mapping methods in a relatively large sample of INPH patients [10]. The aims of the study are 1) to evaluate differences in DTI measures, including FA, AD, RD, and MD, in INPH patients relative to the outcome of their CSFTT and 2) to investigate relationships between DTI indices and various clinical profiles in INPH patients. We hypothesized that the topographical DTI features may be different according to CSFTT response, and there may be unique relationships between DTI findings and clinical characteristics.

2. Methods

2.1. Participants

Participants were prospectively recruited from patients who visited the Center for Neurodegenerative Diseases of Kyungpook National University Medical Center, South Korea from July 2011 to November 2014. This study was approved by the Institutional Review Board at our institution. The diagnosis of INPH was made using the criteria proposed by Relkin et al. [11].

2.2. Assessing illness severity

The patients' general cognitive state and severity of dementia were evaluated by means of the Korean-MMSE (K-MMSE) and Clinical Dementia Rating Scale (CDR) [12,13]. The Trail Making Test Part A (TMT-A) is a common neuropsychological test to evaluate psychomotor speed [14].

The INPHGS is a clinician-rated scale to assess the severity of each fundamental symptom of INPH (cognitive impairment, gait disturbance and urinary disturbance) after an unstructured interview with patients and caregivers [15].

The gait assessment included measurements of time on the Timed Up and Go (TUG) test and 10 m walking test [15–18]. The features of gait disturbance related to INPH were also estimated using the Gait Status Scale (GSS) [15]. And, we assessed parkinsonism severity using the Unified Parkinson's Disease Rating Scale (UPDRS).

2.3. CSFTT

A lumbar tap removing 30–50 ml of CSF was performed on all INPH patients. After the tap, all patients were re-evaluated using the INPHGS, which is a validated scale for the measurement of INPH symptom severity, and the TUG test. Changes in gait were evaluated 1 day after the tap, while changes in cognition and urination were evaluated at one week [19]. Responses to the CSFTT were defined using these scales. The following criteria were used to identify responders: improvement of one point or more on the INPHGS or more than 10% improvement in time on the TUG test [8,19].

2.4. MRI Acquisition and data processing

MRI data were obtained using a 3.0 Tesla system (GE Discovery MR750, GE Healthcare). The DTI data were obtained from the INPH patients using a single-shot echo-planar acquisition with the following parameters: 45 noncollinear diffusion gradient directions; TR = 9900 ms; TE = 76 ms; acquisition matrix = 128 × 128; field of view = 240 mm; slice thickness = 2 mm without a gap; flip angle = 90°; b-factor = 600 s/mm^2.

All DTI data were preprocessed using the FMRIB's software Library program (FSL, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL). First, head motion artifacts and eddy current distortions in the DTI data were corrected by applying affine transformation to their first non-diffusion-weighted (b0) image. Skull stripping was performed by removing non-brain structures using the Brain Extraction Tool. Thereafter, FA, AD, RD, and MD maps were estimated by fitting a diffusion tensor model to each image voxel of the preprocessed DTI data.

2.5. Tract-based atlasing

The Johns Hopkins University white matter tractography atlas was mapped to the diffusion data of each subject to identify the following regions of interest (ROIs): anterior thalamic radiation (ATR), CST, cingulum–cingulate gyrus (CgC), cingulum–hippocampus (CgH), inferior fronto-occipital fasciculus (IFO), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), SLF temporal component (tSLF), and uncinate fasciculus (UNC) within each hemisphere, and the forceps major (Fmajor) and forceps minor (Fminor) across hemispheres [10,20]. Since ROI-specific mean FA, AD, RD, and MD values were estimated within each subject's native space, a T2-weighted reference brain image from the Johns Hopkins University tractography atlas was spatially aligned to each subject's b0 image using a hierarchical multi-scale non-linear fitting algorithm [21]. These transformations were applied to each ROI in the Johns Hopkins University atlas, essentially resulting in ROIs within each subject's native space. It was inspected visually to ensure that automatically generated labels corresponded well to individual brain anatomy. Subsequently, mean FA, AD, RD, and MD values were computed within each ROI.

2.6. Statistical analyses

Statistical analyses were conducted using IBM SPSS Statistics for Windows (version 21.0). We used an independent *t*-test for the comparison between CSFTT responders and non-responders in mean FA, AD, RD, and MD for 20 track-based ROIs. A Bonferroni's correction was used to control for multiple comparisons. Uncorrected results are also presented [22,23], because a Bonferroni's correction is quite conservative [24]. Pearson's or Spearman's correlations were employed to investigate the relationship between clinical measures and DTI indices in INPH. The correlations with $p < 0.01$ ware considered to be significant.

3. Results

3.1. CSFTT responders versus non-responders in INPH patients

The 54 INPH patients constituted the final sample for analysis. The baseline clinical findings of the study cohort are shown in Table 1. There were no differences between the responders and the non-responders with regard to sex ratios, age, duration of symptoms, educational level, cerebrovascular risk factors such as hypertension, diabetes, and lipid disorder, initial symptoms, full-blown symptoms, drainage volume of CSF and opening pressure during the tap test, and apolipoprotein E ε4 allele frequency. And, we did not find any significant differences in the measurement of gait and cognitive disturbances between these groups. MRI findings, including Evan's ratio and the narrowing of the CSF space at the high convexity, did not differ between the responders and non-responders.

However, concerning DTI parameters (Table 2 and Fig. 1), uncorrected results revealed that the CSFTT non-responders in INPH patients exhibited lower FA in the left ATR, left CgH, and left IFO in comparison with CSFTT responders. Uncorrected results also revealed that the CSFTT non-responders, when compared to responders, showed higher AD, RD, and MD in the left CgH and left ILF. After Bonferroni's correction, the differences in FA, AD, RD, and MD between responders and non-responders did not reach statistical significance.