Diffusion Tensor Imaging of Idiopathic Normal Pressure Hydrocephalus: A Voxel-Based Fractional Anisotropy Study

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Abstract

Diffusion tensor imaging (DTI) using a 3.0 tesla magnetic resonance scanner was used to investigate white matter changes caused by idiopathic normal pressure hydrocephalus (INPH) in 10 patients diagnosed by clinical symptoms (gait disturbance, dementia, and/or urinary incontinence) and Evans index > 0.3, and compared with findings for 10 age-matched controls (≥ 60 years). Then, using a computer-automated method, fractional anisotropy (FA) brain maps were generated and finally transformed into the standard space. Voxel-based FA values within two regions of interests (ROIs), the forceps minor and corticospinal tracts, were then separately evaluated. Within each ROI, statistical comparisons of results from the INPH and control groups were performed. In addition, for INPH patients, grading scores for clinical symptoms and FA values were correlated. The forceps minor mean FA value was much smaller for the INPH group (0.504) than for the control group (0.631). The corticospinal tract mean FA value was slightly smaller for the INPH group (0.588) than for the control group (0.632). Additional analyses indicated that lower FA values within the forceps minor tended to be associated with clinical symptoms such as urinary incontinence and gait disturbance. Our findings indicate FA values decreased in the forceps minor of INPH patients. We also found that lower values were associated with severer clinical symptoms, implying that DTI techniques may be developed for more accurate diagnosis.

Key words: dilatation, elderly, neuroimaging, shunt, ventricle

Introduction

Idiopathic normal pressure hydrocephalus (INPH) is a neural syndrome that afflicts elderly people. The clinical manifestations are gait disturbance, dementia, and urinary incontinence without preceding disorders.¹⁾ Patients with these symptoms often need care to cope with the activities of daily living,^{8,21)} so adequate diagnosis and treatment (e.g., ventriculo-peritoneal shunt or lumbo-peritoneal shunt)²⁸⁾ are essential to reduce medical and social-welfare costs in countries with aging populations. The diagnosis is based on clinical observations supported by computed tomography (CT) and magnetic resonance (MR) imaging, and other neuroradiographical examina-

tions.⁴⁾

Ventricular dilation is a critically important neuroradiographical finding: an Evans index, the ratio of the maximum width of the frontal horns to the maximum width of the inner table of the skull, of greater than 0.3 is accepted as an essential diagnostic criterion for INPH.^{31,32)} In addition, recent MR imaging studies have indicated that tightness of the high parietal convexity is commonly observed in INPH patients.^{5,18,35)} Such anatomical changes in the cerebrospinal fluid (CSF) space have been widely accepted as neuroradiographical evidence justifying the diagnosis of INPH.

Detection of deep white-matter lesions is another important neuroradiographical finding commonly observed in INPH patients.^{24,32)} Diffusion tensor imaging (DTI), a newly developed MR technique, has been recently applied to evaluate white matter de-

generation in INPH patients.^{6,9,20,22,27)} DTI can sensitively detect the direction of diffusion of water molecules and so reveals the orientation of the white matter tracts.³⁶⁾ This anatomical detail enables clinically useful characterization of the degeneration of neural fibers affected by various neural diseases.³⁷⁾ Recent studies based on fractional anisotropy (FA) values in some brain regions, including the corpus callosum and corticospinal tracts, have reported that patients with INPH exhibit white matter changes.^{6,20,22,27)} Quantitative analysis of FA values would be useful to better characterize the white matter changes in INPH patients.^{6,20)}

The present study used a computer-automated technique for FA evaluation and showed that, compared with control subjects in a similar age range, FA values in the forceps minor (anterior portion of corpus callosum) were much lower in INPH patients and that low values were associated with more severe clinical manifestations.

Methods

This study recruited both INPH patients and control subjects from patients who visited our outpatient clinic between May 2010 and May 2011. All subjects (or, if more appropriate, relatives) provided written consent for inclusion in the study.

The INPH patients presented with gait disturbance or dementia or urinary incontinence or combinations of these symptoms. Our routine protocol included MR imaging, electrocardiography, chest radiography, and blood sampling. After obtaining informed consent, eligible patients then admitted to our hospital and underwent removal of 30 ml CSF via a lumbar puncture (tap test).⁵⁾ The inclusion criteria were age ≥ 60 years, presence of one or more INPH symptoms, Evans index greater than 0.3, absence of known disorders causing ventriculomegaly, and normal CSF findings (protein ≤ 50 mg, cell count ≤ 3 mm³, and pressure ≤ 20 cmH₂O)⁵⁾; such criteria were identical to possible INPH as stipulated in the Japanese guidelines for INPH.⁴⁾

The control subjects had chief complaints of headache or dizziness or both, but with no meaningful findings after medical examinations such as CT and blood analysis, and whose symptoms were alleviated within a 2-week follow-up period. Other inclusion criteria were age ≥ 60 years, absence of neurological symptoms, and no history of neurological disorder.

MR imaging was typically performed 2 to 4 weeks after the initial visit to our outpatient clinic, using a 3.0 tesla MR scanner (Trio; Siemens AG, Erlangen, Germany) with a 32-channel head coil. The DTI

scheme included acquiring 12 images with non-linear diffusion gradients ($b = 1000$ sec/mm²) and one non-diffusion-weighted image ($b = 0$ sec/mm²), employing a single-shot echo-planar imaging sequence. A total of 64 axial slices were obtained from each patient. The field of view was 230.4 mm $\times$ 230.4 mm, the acquisition matrix was 128 $\times$ 128, and the slice thickness was 3 mm without a gap, which resulted in voxel-dimensions of 1.8 mm $\times$ 1.8 mm $\times$ 3.0 mm. Echo time was 83 msec and repetition time was 7000 msec. T₂-weighted images were obtained using a spin-echo sequence. The field of view was 218.88 mm $\times$ 218.88 mm, the acquisition matrix was 192 $\times$ 192, and the slice thickness was 3 mm without a gap, which resulted in voxel-dimensions of 1.14 mm $\times$ 1.14 mm $\times$ 3.0 mm. Echo time was 88 msec and repetition time was 5000 msec. A total of 50 axial slices were obtained from each patient. In addition, T₁-weighted MR images were also obtained for other diagnostic purposes. The total time for MR imaging acquisition was approximately 20 minutes per patient. Patients whose inability to stay still prevented complete MR imaging acquisition were also excluded from our database.

The brain image analysis package FMRIB Software Library (FSL), comprising various tools including Brain Extraction Tool (BET), FMRIB's Diffusion Toolbox (FDT), FMRIB's Linear Image Registration Tool (FLIRT), FMRIB's Nonlinear Image Registration Tool (FNIRT), FSLUTILS (miscellaneous FSL utilities for converting and processing images), and FSLView (interactive display tool for three-dimensional and four-dimensional data), was used for image processing.^{16,34)} The FDT tool was used to align all images in volumetric relation to the first image ($b = 0$ sec/mm²), and DTI data were corrected for motion and eddy current distortion.¹⁷⁾ Then, extra-cerebral matter was excluded from the images using the BET tool.¹⁵⁾ Next, to evaluate tensor diffusion and calculate each patient's brain FA values, DTI was analyzed using the FDT tool (FA brain map). Using FLIRT and FNIRT,^{13,14)} the FA values were mapped to standard stereotaxic space [International Consortium of Brain Mapping [ICBM] DTI-81 Atlas].^{19,29)} To keep the transformation procedure simple, as recommended in the manual, this study employed standard tasks settings for FNIRT.¹³⁾ Spatial transformations of the FA brain maps were confirmed by visual comparison with images generated by FSLView.¹²⁾ The same image processing procedures were used as in our previous study.²³⁾

This study employed the ICBM DTI-81 Atlas to establish the standard stereotaxic space.^{19,29)} Using FSLUTILS,¹¹⁾ the forceps minor (anterior portion of

Fig. 1 Representative magnetic resonance images for typical cases. T₂-weighted images (left column) and fractional anisotropy (FA) brain images in standard space (right column). Region of interest is shown in blue (forceps minor) or red (corticospinal tracts). A: Case 1. B: Case 5, C: Case 10, D: Case 11, E: Case 15, F: Case 20.

corpus callosum) white matter tracts and bilateral corticospinal tracts were separately abstracted from the ICBM DTI 81 brain map (Fig. 1). FA values within regions of interest (ROIs) were assessed and mean values for single voxels were then calculated using FSLUTILS.

To classify the symptoms of INPH patients, and to score cognitive, gait, and urinary functions, we employed the INPH grading scale (from 0, normal to 4, severe disability),²⁵⁾ and the modified Rankin scale (mRS) to score activities of daily living (from 0, normal to 5, severe disability).³³⁾

Effects of the tap test were evaluated from before-and-after results of the 3-meter up-and-go tests.³⁰⁾ These tests were conducted on the day before, and 3 hours and 1 week after the tap test. To index the effects of the tap test, we evaluated improvements in the up-and-go test results by calculating the ratio between best performance (in seconds) either 3 hours or 1 week after the tap test and the performance value before. Besides the up-and-go test, we also performed mini-mental state examination (MMSE)³⁾ and scored the frontal assessment battery (FAB).²⁾ For clarity, results from MMSE and FAB were not

included in the analytical database.

For comparisons between the INPH group and the control group, conventional t-tests were separately performed within ROIs (forceps minor and corticospinal tracts). To evaluate the relationships between clinical symptoms and FA values in INPH patients, Spearman's rank correlation tests were used to compare FA values and INPH grading scale and mRS scores separately within ROIs. P values of less than 0.05 were considered statistically significant.

Results

Table 1 presents the patient profiles. Age ranged from 69 to 82 years (mean $\pm$ standard deviation 75.1 ± 4.5 years) for INPH patients and from 61 to 79 years (68.8 ± 7.5 years) in the control group. Table 2 shows the tap test results. Except for Case 3, all patients showed more than 10% improvement (ratio < 0.9) in up-and-go time after the tap test.

Figure 1 shows MR imaging findings for typical cases. T₂-weighted imaging clearly showed ventricular dilation in patients with INPH symptoms. FA

Table 1 Patient profiles

Case No.	Age (yrs)	Sex	Group	mRS	INPH grading scale*	FA value	
						Forceps minor	Corticospinal tracts
1	79	F	INPH	3	2: 2: 1	0.582	0.642
2	74	F	INPH	2	1: 1: 1	0.561	0.565
3	70	M	INPH	2	0: 2: 1	0.557	0.632
4	77	M	INPH	4	3: 3: 3	0.543	0.598
5	82	M	INPH	4	3: 3: 4	0.520	0.628
6	74	F	INPH	3	2: 3: 3	0.489	0.566
7	72	M	INPH	3	1: 2: 3	0.477	0.602
8	81	F	INPH	4	1: 3: 3	0.476	0.577
9	69	M	INPH	4	1: 3: 3	0.471	0.558
10	73	F	INPH	4	3: 3: 3	0.444	0.562
11	67	M	control	—	—	0.685	0.671
12	61	M	control	—	—	0.682	0.668
13	64	F	control	—	—	0.678	0.670
14	64	F	control	—	—	0.646	0.633
15	61	F	control	—	—	0.636	0.629
16	79	M	control	—	—	0.626	0.614
17	79	F	control	—	—	0.604	0.632
18	64	F	control	—	—	0.600	0.622
19	70	M	control	—	—	0.556	0.651
20	79	F	control	—	—	0.525	0.625

Separately within each group, patients are ordered according to forceps minor fractional anisotropy (FA) value (greater to smaller). Modified Rankin scale (mRS) and idiopathic normal pressure hydrocephalus (INPH) grading scale were assessed on the first visit to our outpatient clinic. *Scores for cognitive impairment: gait disturbance: urinary incontinence. F: female, M: male.

Table 2 Tap test results

Case No.	Before (sec/steps)	3 Hours after (sec/steps)	1 Week after (sec/steps)	Ratio
1	21.3/35	15.3/30	21.4/36	0.71
2	13.2/23	12.7/22	11.6/20	0.88
3	10.0/15	9.5/14	9.8/14	0.95
4	22.5/42	19.8/39	24.5/47	0.88
5	33.1/50	35.6/67	23.3/43	0.70
6	17.0/21	13.3/20	16.4/22	0.78
7	11.5/24	9.6/19	9.9/23	0.83
8	37.1/49	30.7/39	28.6/43	0.77
9	18.3/26	14.9/23	14.1/23	0.77
10	43.9/72	47.7/70	36.8/63	0.84

Best performance after the tap test shown in bold.

brain images from INPH patients were successfully transformed into the standard space despite the potentially confounding effects of altered morphology, comparable to those from the control group. Defined in the standard space, both the forceps minor and corticospinal tract ROI templates were a close fit to the FA brain images from the INPH and control groups.

Figure 2 shows statistical comparisons of FA values in the INPH and control groups. Within both

ROIs, FA values were significantly lower in the INPH group than in the control group. Within the forceps minor, the mean FA value was 0.504 for the INPH group and 0.631 for the control group, indicating that mean FA for INPH patients was approximately 20% lower. In the corticospinal tracts, the mean FA value was 0.588 for the INPH group and 0.632 for the control group, showing an approximately 7% difference. FA values from the forceps minor provide stronger evidence of INPH than values from the corticospinal tracts.

Table 3 shows the correlations between FA values and clinical manifestations. FA values within the forceps minor were significantly correlated with urinary incontinence ($p = 0.023$). Within this ROI, lower FA values tended to correlate with gait disturbance ($p = 0.066$). No such relationships were apparent after analyzing data from the corticospinal tracts.

Discussion

The present comparison of FA values in INPH patients and control subjects observed that INPH FA values within the forceps minor were approximately 20% lower. In addition, data analyses revealed a ten-

Fig. 2 Comparisons of fractional anisotropy (FA) values within the forceps minor (left) and corticospinal tracts (right) of patients with idiopathic normal pressure hydrocephalus (INPH) and control subjects. * $p = 0.0009$, ** $p = 0.0001$.

Table 3 Correlations between fractional anisotropy values and symptoms graded by idiopathic normal pressure hydrocephalus (INPH) grading scale and modified Rankin scale (mRS)

Region of interest	Symptom grading	Coefficient	p Value
Forceps minor	mRS	-0.579	0.079
	INPH grading scale		
	cognitive impairment	-0.128	0.724
	gait disturbance	-0.601	0.066
	urinary incontinence	-0.705	0.023
Corticospinal tracts	mRS	-0.219	0.544
	INPH grading scale		
	cognitive impairment	0.005	0.988
	gait disturbance	-0.198	0.584
	urinary incontinence	-0.269	0.452

Bold indicates statistical significance.

dency for forceps minor FA values to decrease with more severe clinical manifestations of INPH.

The brain images of INPH patients usually show a wide range of individual variability because of ventricular dilation, and this has made inter-subject analysis of images technically difficult.³⁵⁾ To meet this challenge, we attempted to apply computer-automated standardization of brain images. As shown in Fig. 1, this standardization could transform FA brain images from INPH patients into the standard space as successfully as images from the control group. We were then able to perform inter-subject analyses of FA brain images.

In our population, the mean age of the control group was slightly lower than that of the INPH group. Therefore, the observed differences in FA could be simply attributed to the age difference. Indeed, several reports have provided evidence that FA values naturally decrease with normal aging.^{10,26)} However, our findings show an approximately 20%

decrease in FA values within the forceps minor of the INPH patients. A difference of this magnitude cannot be attributed to the influence of normal aging.^{10,26)}

Several previous studies have shown that INPH patients exhibit lower FA values in the frontal areas, including the forceps minor, than normal subjects.^{6,27)} In addition, our analyses revealed some association of lower FA values in these areas with the clinical symptoms of INPH (Table 3). Taken together, these findings suggest that neural degeneration in these areas could contribute to the essential pathology that causes INPH symptoms. Therefore, FA values could be used for the diagnosis of INPH, but a careful study of more subjects is needed to define a cut-off point and assess the sensitivity and specificity.

Slightly, but statistically significantly, lower FA values were observed within the corticospinal tracts. This finding conflicts with previous studies that reported higher FA values within the corticospinal tracts for INPH patients than for normal subjects.^{6,22)} Such changes were even reversible after shunt implantation.²²⁾ This could mean that higher corticospinal tract FA values may be important to better characterize INPH white matter changes. Recently, DTI tractography showed that neural fibers in corticospinal tracts were compressed by ventricular dilation, resulting in higher FA values for INPH patients.⁷⁾ The discrepancy may be attributed to the differences in the processes for the brain image analyses, as our study employed spatial transformation into the standard brain. Further study is required to explain these discrepancies.

Regarding the effectiveness of the tap test, the Japanese Guidelines for INPH (2004) stipulate a more than 10% improvement in the up-and-go test.⁴⁾ In the present study, all tested patients except for

Case 3 met the stipulation: Case 3 also achieved the best initial results (10 sec for 15 steps), and ceiling effects are likely to account for the lack of adequate improvement.³⁰⁾ Thus, we are confident that our population generally responded well to the tap test, confirming the reliability of our population sample.

This study has a number of limitations. First, the sample size was relatively small (10 persons each for the INPH and control groups). Even so, our analyses yielded statistically significant findings (Fig. 2 and Table 3). Second, we recruited patients with no history of Parkinson's disease, Alzheimer's disease, or other geriatric neural disorders. However, we often encounter patients with overlapping histories of multiple geriatric neural disorders in clinical practice. To better inform clinical practice, comparative studies including these neural disorders is needed.²⁰⁾ Third, this study did not further analyze the relationships between FA values and the effects of the tap test. Although the Japanese Guidelines for INPH (2004) stipulate criteria, their validity and reliability have yet to be established.⁴⁾ Future studies are needed to clarify this issue.

In summary, this study showed that FA values within the forceps minor were significantly lower in INPH patients and tended to correlate with the severity of clinical symptoms. This observation suggests that DTI may prove clinically useful in the diagnosis of INPH.

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