

White Matter Characteristics of Idiopathic Normal Pressure Hydrocephalus: A Diffusion Tensor Tract-Based Spatial Statistic Study

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Abstract

Using magnetic resonance-diffusion tensor imaging (DTI), we examined white matter changes within the brains of patients diagnosed with idiopathic normal pressure hydrocephalus (INPH). We analyzed data for 24 INPH patients who were presented with typical clinical symptoms (gait disturbance, dementia, and/or urinary incontinence) and Evans index > 0.3, and compared these with the control data from 21 elderly persons (≥ 60 years). DTI brain images were obtained with a 3T scanner. Fractional anisotropy (FA) brain maps were generated using a computer-automated method, and tract-based spatial statistics (TBSS) were then applied to compare the FA brain maps of the INPH and control groups in standard space. The TBSS data were further investigated using region-of-interest (ROI) analyses. ROIs were set within the corpus callosum, the posterior limb of the internal capsule (PLIC), and the cerebral peduncle in reference to a standard brain template. Compared with the control group, FA values in the INPH group were significantly lower in the corpus callosum and just significantly higher in the PLIC, but no significant differences were evident in the cerebral peduncle. The much lower FA values in the corpus callosum, but not the slightly higher FA values in the PLIC, were associated with more severe clinical symptoms such as gait disturbance. The lower FA values in the corpus callosum may offer a clue to solve the pathophysiology of INPH.

Key words: dementia, elderly, gait, incontinence, ventricle

Introduction

Idiopathic normal pressure hydrocephalus (INPH) is a neural syndrome that afflicts many elderly people. Its clinical manifestations are cognitive impairment (dementia), gait disturbance, and urinary incontinence without any preceding disorders.¹⁾ As in most other advanced countries, in Japan the rapidly increasing elderly population has become a serious social issue and several reports have put the prevalence of INPH in the elderly population at 0.5–2.9%.^{5,15,17,36)} As patients with INPH often need assistance for activities of daily living,^{14,20)} adequate diagnosis and treatment are essential to reducing medical and social-welfare costs in countries with aging populations.²⁶⁾

Diffusion tensor imaging (DTI), a magnetic resonance (MR) technique, has recently been applied

to evaluate white-matter degeneration in patients with INPH.^{11–13,16,19,21,22,24,31)} Among the parameters obtained from DTI, fractional anisotropy (FA) has proven useful as an index of white-matter axonal degeneration. Previous DTI studies on INPH have reported altered FA values within various supratentorial regions.^{11–13,19,21,22,24,31)} The vast majority of these studies observed lower FA values in the corpus callosum than in normal controls.^{11,12,21,22,24)} Beside lower FA values in the corpus callosum, some previous studies also noted that FA values in the corticospinal tract, including the posterior limb of the internal capsule (PLIC), were rather higher and were correlated with more severe clinical manifestations.^{11,21)} In a DTI tractography study, Hattori et al.¹²⁾ suggested that higher FA values in the PLIC could be attributed to compression of neural fibers by ventricular dilatation, which is a neuroradiological feature of INPH.¹³⁾

As suggested by these previous findings, DTI-FA

is a potentially useful tool for the diagnosis of INPH. However, few other studies have actually systemically analyzed whole brain FA values and assessed the relationship between FA changes and clinical manifestations. Therefore, in this study we performed tract-based spatial statistics (TBSS) on DTI-FA data and quantitatively assessed regional changes in FA in relation to clinical severity.

Methods

Subjects

Between May 2010 and April 2012, we sampled both INPH patients and control subjects. Candidates for this study were all patients who visited our outpatient clinic. All subjects (or, if more appropriate, relatives) provided written consent for inclusion in the study.

For the INPH group, we recruited patients who presented with cognitive impairment, gait disturbance, urinary incontinence, or combinations of these symptoms. Our routine protocol consists of magnetic resonance imaging (MRI) scans, electrocardiograms, chest X-rays, and blood sampling. After obtaining informed consent, eligible patients were admitted to our hospital for removal of 30 ml of cerebrospinal fluid (CSF) via lumbar puncture (spinal tap).¹⁸⁾ After confirming normal CSF findings (protein \leq 50 mg/dl, cell count \leq 3/mm³, and pressure \leq 20 cm H₂O),¹⁰⁾ data from patients were recorded into our analytic database if they were aged \geq 60 years, presented with one or more INPH symptom, had an Evans index value $>$ 0.3, and had no known disorders that might cause ventriculomegaly. To classify the symptoms of INPH patients, we employed the INPH grading scale (0 = normal, 4 = severe disability) to score cognitive, gait, and urinary functions²³⁾ and the modified Rankin Scale (mRS) to score activities of daily living (0 = normal, 5 = severe disability).³⁷⁾ Effects of the spinal tap were evaluated by comparing pre and post results for the 3m Timed Up and Go Test (TUG).^{22,29)} To provide control data, we recruited patients whose chief complaint was headache or dizziness or both, and for whom the results of medical examinations such as CT and blood analysis were inconclusive, and whose symptoms were alleviated within a 2-week follow-up period. Other inclusion criteria were age \geq 60 years, absence of neurological symptoms, and no history of neurological disorder.

The work presented here extends that of our previously published study,²²⁾ which included data from 10 INPH and 10 control cases, already input into the database used by the present study. The previous study was designed to establish automated computer image analysis of the INPH brain images

with morphological diversity (i.e., ventricle dilatation). The results indicated that transformation of FA brain images were successful enough to allow inter-subject analysis in standard space.²²⁾

MRI acquisition

The MRI acquisition series was typically performed 2 to 4 weeks after the initial visit to our outpatient clinic. All MR images were obtained using a 3.0 Tesla MR scanner (Trio: Siemens AG, Erlangen, Germany) with a 32-channel head coil.

The DTI scheme consisted of acquiring 12 images with non-collinear diffusion gradients ($b = 1000$ s/mm²) and one non-diffusion-weighted image ($b = 0$ s/mm²), employing a single-shot echo-planar imaging sequence. Sixty-four contiguous 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, which resulted in voxel dimensions of 1.8 mm \times 1.8 mm \times 3.0 mm. Echo time was 83 ms and repetition time was 7,000 ms. Contiguous 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, which resulted in voxel dimensions of 1.14 mm \times 1.14 mm \times 3.0 mm. Echo time was 88 ms and repetition time was 5,000 ms. Fifty such axial slices were obtained from each patient. In addition, T1-weighted MR images were also obtained for other diagnostic usage. The total time for MRI acquisition was approximately 20 min per patient.

Image processing

The brain image analysis package FSL (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>), comprising various tools including BET, FDT, FNIRT, and FSLUTILS, was used for image processing.^{33,40)} The FDT tool was used to correct motion and eddy current distortions by aligning all images to the first image ($b = 0$ s/mm²) and the BET tool was used to exclude extra-cerebral matter from the images. Finally, to evaluate tensor diffusion and calculate brain FA values for each patient, DTI data was analyzed using the FDT tool (FA brain map).

Tract-based spatial statistics

The TBSS module of FSL was used to outline the brain regions exhibiting neural fiber degeneration associated with INPH. It allows the study of cerebral white matter by using the intrinsic anisotropic properties of the white matter to project the FA of local tract structures onto a virtual skeleton, thereby providing an alignment-invariant tract representation of the median part

of the tract.³²⁾ To keep the procedures simple, the default settings recommended in the TBSS manual (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS>) were used. In brief, FA maps for each participant were registered into a standard brain template (FMRIB58_FA, part of the FSL suite) using the non-linear spatial transformation tool FNIRT. A mean FA image was then compiled by averaging aligned FA maps from each participant. Then, to generate a mean FA skeleton representing the centers of all tracts common to the group, the map threshold was set for voxels showing FA values ≥ 0.2 . Aligned FA data for each participant were projected onto the standard skeletonized FA image (FMRIB58_FA-skeleton, packaged in FSL) by searching the area around the skeleton in the direction perpendicular to each tract, finding the highest local FA value, and assigning this value to the skeleton (Fig. 1).³²⁾ Then, voxel-wise spatial statistical analysis comparing the INPH and control groups was carried out using the “randomize” program within FSL, which performs permutation testing.²⁷⁾ Thresholding was carried out using threshold-free cluster enhancement, a new method for finding significant clusters in MRI data without having to define them as binary units.³⁴⁾ Clusters were assessed for significance at $P < 0.05$, fully corrected for multiple comparisons across space.

Region of interest analysis

For the quantitative assessment of neural degenera-

tion within the brain, each participant’s aligned FA image was projected onto the mean FA skeleton.²⁸⁾ Then using FSLUTILS, regions of interest (ROIs) were abstracted with reference to the standard brain for white matter (Johns Hopkins University DTI White-Matter Atlas).³⁸⁾ ROIs were set within the corpus callosum, PLIC, and cerebral peduncle (Fig. 2).

Mean FA values for these voxels were then calculated.^{6,30,35)} The derived FA values within each ROI were then statistically compared (t -test, $P < 0.05$) between the INPH and control groups.

To evaluate the relationship between clinical symptoms (INPH grading scale and mRS) and FA values for the INPH patients, Spearman’s rank correlation tests were performed separately for each ROI. A P value less than 0.05 was considered statistically significant.

Results

Table 1 shows the profiles of the 24 INPH and 21 geriatric control participants who were enrolled in this study. All patients with INPH exhibited gait disturbance and had positive results after the spinal tap. Figure 1 shows the MRI data for representative cases. For the representative case from the INPH group, T2 weighted images clearly show ventricular dilatation. Despite the potentially confounding effects of altered morphology, FA brain images from the INPH patients were as successfully transformed into standard space as images from the control group.

Figure 3 shows the results obtained from TBSS of the comparison between the INPH and control FA brain maps. Blue areas indicate regions showing

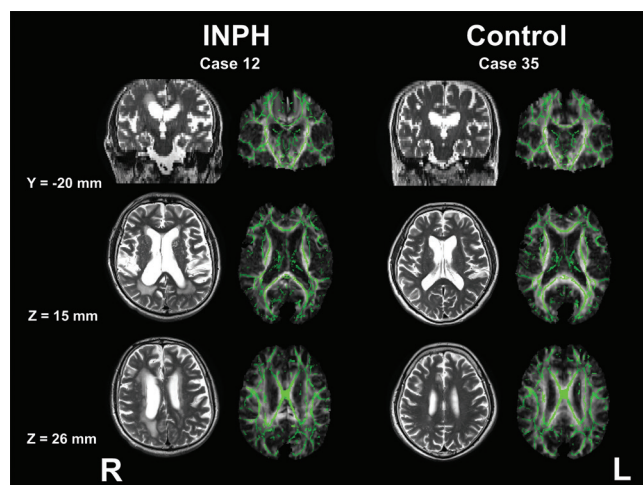


Fig. 1 Representative magnetic resonance brain images from typical cases (see Table 1 for case numbers). For each example, left column shows T2 weighted images and right column shows fractional anisotropy (FA) brain images in standard space (skeletonized FA maps shown in green). L: left, R: right. Slices are coordinated with standard space (Y and Z axes in mm).

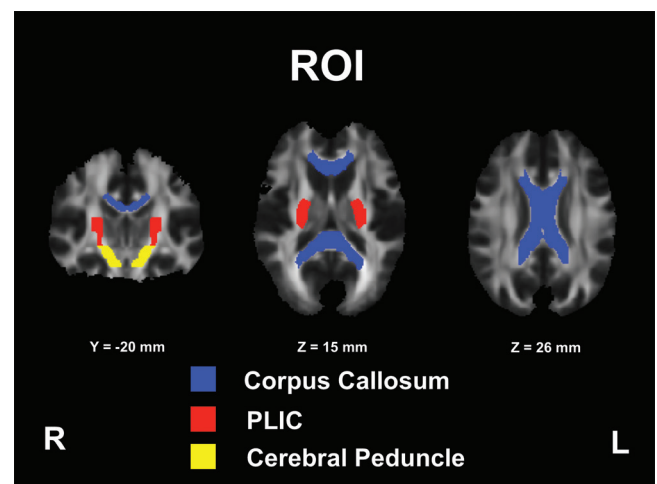


Fig. 2 Regions of interest. Slices are coordinated with standard space (Y and Z axes in mm). PLIC: posterior limb of internal capsule. L: left, R: right.

Table 1 Patients' profile

Case No.	Age (yrs)	Sex	Group	mRS	INPH grading scale			FA		
					C	G	I	Corpus callosum	PLIC	Cerebral peduncle
1	78	Female	INPH	2	2	1	2	0.705	0.765	0.690
2	77	Male	INPH	4	3	3	3	0.675	0.746	0.706
3	77	Male	INPH	3	0	3	2	0.666	0.737	0.723
4	66	Female	INPH	2	0	2	0	0.652	0.766	0.691
5	85	Female	INPH	4	2	3	3	0.640	0.709	0.678
6	70	Male	INPH	2	0	2	2	0.638	0.711	0.689
7	81	Female	INPH	3	2	2	1	0.635	0.722	0.669
8	72	Male	INPH	3	1	2	3	0.628	0.706	0.653
9	70	Male	INPH	2	0	2	1	0.626	0.751	0.697
10	74	Female	INPH	2	1	1	1	0.623	0.710	0.664
11	79	Female	INPH	3	2	2	1	0.622	0.756	0.690
12	80	Male	INPH	1	3	1	3	0.618	0.716	0.668
13	81	Female	INPH	4	1	3	3	0.608	0.742	0.670
14	79	Female	INPH	3	1	3	3	0.606	0.739	0.696
15	69	Male	INPH	4	1	3	3	0.605	0.727	0.708
16	76	Female	INPH	2	1	3	0	0.602	0.686	0.651
17	73	Male	INPH	1	0	2	1	0.601	0.732	0.710
18	82	Male	INPH	3	1	2	2	0.597	0.712	0.646
19	81	Female	INPH	4	3	3	4	0.595	0.692	0.674
20	82	Male	INPH	4	3	3	4	0.593	0.744	0.684
21	82	Male	INPH	4	3	3	3	0.589	0.738	0.688
22	73	Female	INPH	4	3	3	3	0.565	0.742	0.678
23	74	Female	INPH	3	2	3	3	0.547	0.719	0.639
24	71	Male	INPH	1	3	3	3	0.519	0.629	0.633
25	61	Male	Control	–	–	–	–	0.767	0.741	0.727
26	64	Female	Control	–	–	–	–	0.750	0.753	0.723
27	61	Female	Control	–	–	–	–	0.749	0.736	0.695
28	64	Female	Control	–	–	–	–	0.729	0.701	0.699
29	82	Male	Control	–	–	–	–	0.729	0.732	0.687
30	80	Female	Control	–	–	–	–	0.728	0.704	0.681
31	75	Female	Control	–	–	–	–	0.727	0.709	0.683
32	79	Male	Control	–	–	–	–	0.723	0.670	0.683
33	67	Male	Control	–	–	–	–	0.709	0.712	0.728
34	76	Male	Control	–	–	–	–	0.699	0.708	0.692
35	70	Male	Control	–	–	–	–	0.690	0.744	0.728
36	72	Female	Control	–	–	–	–	0.678	0.650	0.676
37	64	Female	Control	–	–	–	–	0.677	0.710	0.677
38	73	Female	Control	–	–	–	–	0.669	0.720	0.672
39	80	Female	Control	–	–	–	–	0.666	0.667	0.658
40	86	Male	Control	–	–	–	–	0.661	0.700	0.687
41	79	Female	Control	–	–	–	–	0.650	0.717	0.675
42	79	Female	Control	–	–	–	–	0.646	0.699	0.693
43	78	Female	Control	–	–	–	–	0.645	0.668	0.657
44	84	Female	Control	–	–	–	–	0.603	0.739	0.655
45	77	Male	Control	–	–	–	–	0.583	0.674	0.644

Separately within each group, patients are ordered according to corpus callosum fractional anisotropy (FA) values (greater to smaller). Modified Rankin Scale (mRS) and idiopathic normal pressure hydrocephalus (INPH) grading scale (C: cognitive impairment, G: gait disturbance, I: urinary incontinence) were assessed on the first visit to our outpatient clinic. PLIC: posterior limb of the internal capsule.

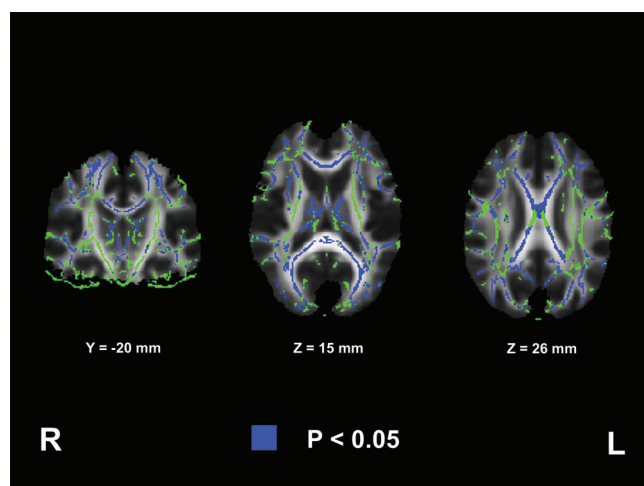


Fig. 3 Results from tract-based spatial statistics for comparison between the idiopathic normal pressure hydrocephalus (INPH) and control groups. L: left, R: right.

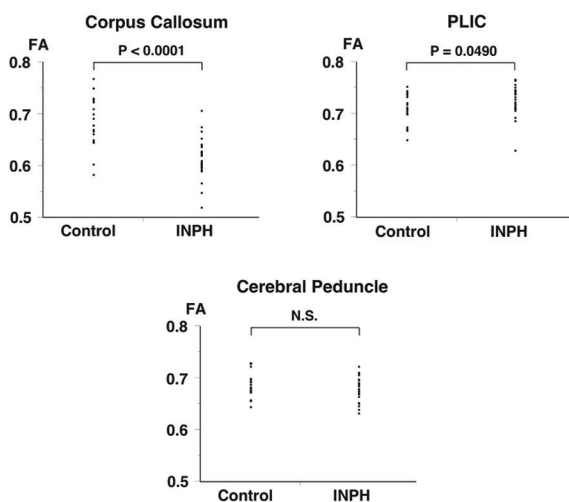


Fig. 4 Comparison of fractional anisotropy (FA) values between idiopathic normal pressure hydrocephalus (INPH) and control groups.

significantly less FA for the INPH patients. FA deficit was most conspicuous in the corpus callosum. By contrast, TBSS did not detect any significant clusters of voxels with higher FA values for the INPH group than the control group (images not shown).

Figure 4 shows the results obtained from ROI analysis performed on individual skeletonized FA brain maps. In the corpus callosum, FA values were significantly lower in the INPH group (mean 0.615; range 0.519–0.705) than in the control group (mean 0.689; range 0.583–0.767; $P < 0.0001$). Conversely, in the PLIC, FA values were just significantly higher in the INPH group (mean 0.725; range 0.629–0.766) than

Table 2 Correlations between fractional anisotropy values and symptoms scored by INPH grading scale and mRS

Region of interest	Symptom grading	Coefficient	P value
Corpus callosum	mRS	-0.132	0.539
	INPH grading scale		
	Cognitive impairment	-0.394	0.057
	Gait disturbance	-0.429	0.037
PLIC	Urinary incontinence	-0.401	0.052
	mRS	0.159	0.460
	INPH grading scale		
	Cognitive impairment	-0.070	0.745
Cerebral peduncle	Gait disturbance	-0.110	0.610
	Urinary incontinence	-0.162	0.449
	mRS	0.117	0.587
	INPH grading scale		
	Cognitive impairment	-0.356	0.087
	Gait disturbance	0.035	0.871
	Urinary incontinence	-0.147	0.492

INPH: idiopathic normal pressure hydrocephalus, mRS: modified Rankin Scale, PLIC: posterior limb of the internal capsule.

in the control group (mean 0.707; range 0.650–0.753; $P = 0.0490$). In the cerebral peduncle, no significant differences were observed between the groups (INPH: mean 0.679; range 0.633–0.723; control: mean 0.687; range 0.644–0.729).

Table 2 indicates the relationship between FA values and clinical severity. Spearman's rank correlation coefficients revealed that the smaller FA values were moderately correlated with gait disturbance (correlation coefficient = -0.429 , $P = 0.037$). Although not statistically significant, lower FA values in the corpus callosum tended to be associated with more severe clinical symptoms for both cognitive impairment (correlation coefficient = -0.394 , $P = 0.057$) and urinary incontinence (correlation coefficient = -0.401 , $P = 0.052$). No such relationships were evident for the PLIC or cerebral peduncle data.

Discussion

This is the first study to employ TBSS and undertake quantitative ROI analysis of skeletonized FA brain maps to assess the association between FA values and clinical severity in INPH. The results indicated that, for INPH patients, FA values were clearly lower in the corpus callosum and slightly higher in the PLIC compared to controls. Further quantitative analysis indicated that the lower FA values in the

corpus callosum, but not values in the PLIC, were associated with more severe clinical manifestations.

Based on the observation that FA values decreased in the corpus callosum, a cut-off point for the diagnosis of INPH could plausibly be set. Recently, Fox et al. investigated the reproducibility and reliability of DTI FA values obtained from multiple scanners in different institutions and reported that FA values are relatively consistent.⁷⁾ In addition, Brander et al. have reported FA norms for healthy subjects.⁴⁾ However, given relatively the small patient population (N = 24) in the present study, we are reluctant to suggest any precise diagnostic criterion based on the FA cut-off value. Careful study of a larger population is needed to establish and understand the sensitivity and specificity of any such cut-off criterion.

Besides FA decreases in the corpus callosum, increased FA values in the PLIC have often been reported in INPH studies.^{11–13,21,31)} In line with these studies, the present study found, using ROI analysis of skeletonized FA brain maps, significantly higher FA values in the PLIC for the INPH group (P = 0.0490). However, direct image comparisons with TBSS did not detect any voxels with higher FA values for the INPH group. Such a discrepancy could be attributed to the small differences in FA values in the PLIC between the INPH and control groups (Fig. 4). In addition, FA values in the PLIC were not found to be associated with clinical manifestations (Table 2). Accordingly, in terms of functional impairment, we assume that FA changes in the PLIC are less important than those observed in the corpus callosum in patients with INPH.

In our previous study,²²⁾ instead of TBSS, we employed a non-linear spatial transformation to bring individual FA brain images into standard space and then compared FA values between the INPH and control groups within predetermined ROIs. The results indicated that FA values in the corticospinal tract of INPH patients were slightly lower than those in the control group.²²⁾ As the PLIC contains fibers of the corticospinal tract, the present findings for the PLIC may contradict our previous findings. To evaluate this issue, we preliminarily performed the same analytic procedure on the present dataset and obtained very similar results to our previous study. Accordingly, the differences of calculated FA values can be attributed to some as yet undetermined path dependence between the two analytical procedures. In this study, we applied TBSS that searches for the highest local FA value and assigns this value to the skeleton. Consequently, the FA values calculated from the skeletonized FA maps naturally exceed those from the original FA maps. Another possible reason is the differences obtained in the ROIs. Hattori

et al. reported that, compared to normal controls, the FA values of INPH patients were lower in the lower portion of corticospinal tract and higher in the upper portion.¹²⁾ Similarly, we observed that, for the INPH group compared with the control group, FA values were just significantly higher in PLIC, but not significantly different in the cerebral peduncle (Fig. 4). Taken together, it is quite plausible that higher FA values in relatively narrow portions such as the PLIC can be diminished in wider ROI, such as the whole corticospinal tract.

This study has a number of limitations. First, previous studies have shown that decreased FA values are not specific to patients with INPH; they are also typical in Alzheimer's disease (AD) and Parkinson's disease (PD). Because its clinical manifestation is dementia, AD is an important differential diagnosis for INPH. Several lines of study have reported that the corpus callosum FA declines in AD patients.^{3,9,25)} Meanwhile, PD patients often suffer a gait disturbance similar to that which is presented in INPH.²⁾ Accordingly, Gattellaro et al. have reported lower corpus callosum FA values in PD patients.⁸⁾ In a recent study investigating FA differences in INPH, AD, and PD, Kanno et al. found that INPH patients had the lowest corpus callosum FA values.¹⁹⁾ However, because no studies have yet rigorously assessed the extent of FA decrease quantitatively in INPH compared with AD, PD, and other geriatric neural diseases,³⁹⁾ further studies are needed to clarify this issue. Another limitation was our use of clinically helpful, but still rather coarse, ordinal assessment of INPH symptoms (0 = normal, 4 = severe disability, as shown in Table 1). Although lower FA values in the corpus callosum were generally associated with more severe symptoms (Table 2), significant differences were only apparent for gait disturbance. To enable more sensitive and accurate diagnosis, a more precise evaluation scale could be helpful in future studies.

In summary, this study showed a conspicuous decline in corpus callosum FA in INPH patients. In these patients, decreased FA values were associated with gait disturbance, which is the most frequent clinical manifestation. These findings suggest that low corpus callosum FA values might serve as a diagnostic marker for INPH.

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Conflicts of Interest Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices in the article.

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