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Correlation of callosal angle at the splenium with gait and cognition in normal pressure hydrocephalus

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OBJECTIVE Idiopathic normal pressure hydrocephalus (iNPH) is characterized by ventricular enlargement that deforms the corpus callosum, making the callosal angle (CA) small. The authors aimed to evaluate the clinical usefulness of the CA in different planes in iNPH.

METHODS Forty patients with iNPH were included in the study. As a control group, 241 patients with other neurological diseases and 50 healthy controls were included. The subjects had been seen at the authors' institutions from 2010 to 2020. The Timed Up and Go (TUG) test total time and Mini-Mental State Examination (MMSE) total score were evaluated. CAs were measured in the axial plane at the splenium and genu and in the coronal plane at the anterior commissure and posterior commissure by using 3-dimensional T1-weighted MR images. As other hydrocephalus parameters, the Evans index, frontal-occipital horn ratio, and third ventricular width were also measured in patients with iNPH. Associations between each CA or hydrocephalus parameter and clinical parameters were evaluated. The classification efficacy of each CA in differentiating between iNPH and other neurological diseases and healthy controls was evaluated.

RESULTS The CA at the splenium, but no other hydrocephalus parameters, was correlated with TUG total time or MMSE total score in patients with iNPH. Receiver operating characteristic analysis showed that a CA of 71.1° at the splenium has 90.0% sensitivity and 89.0% specificity in discriminating iNPH from other neurological diseases and healthy controls. Probabilistic tractography analysis showed that neuronal fibers via the splenium connect the superior parietal lobules, temporal lobes, and occipital lobes.

CONCLUSIONS The study results suggest that interhemispheric disconnections at the splenium are, at least in part, responsible for gait and cognitive disturbance in iNPH. The CA at the splenium is a unique morphological feature that correlates with gait and cognition in iNPH, and it is useful for discriminating iNPH from other neurological diseases and healthy controls.

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KEYWORDS callosal angle; normal pressure hydrocephalus; MRI; gait disturbance; cognitive impairment; functional neurosurgery

Idiopathic normal pressure hydrocephalus (iNPH) is a clinical disease entity characterized by gait disturbance, urinary incontinence, and cognitive decline, with no established histopathological hallmarks.[1] The corpus callosum consists of the interhemispheric fibers connecting the bilateral hemispheres and forms part of the roof of the lateral ventricle, which is abnormally enlarged in iNPH. Thus, the corpus callosum is likely to be mechanically damaged in iNPH because of the enlarged lateral ventricle.[2]

ABBREVIATIONS 3DT1 = 3-dimensional T1-weighted; AC = anterior commissure; AD = Alzheimer's disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; ALS = amyotrophic lateral sclerosis; CA = callosal angle; DLB = dementia with Lewy bodies; FAB = Frontal Assessment Battery; HC = healthy control; iNPH = idiopathic normal pressure hydrocephalus; MMSE = Mini-Mental State Examination; MPRAGE = magnetization-prepared rapid acquisition with gradient echo; MS = multiple sclerosis; PC = posterior commissure; PD = Parkinson's disease; PDD = PD with dementia; ROC = receiver operating characteristic; TUG = Timed Up and Go; VIF = variance inflation factor.

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Several iNPH-specific neuroimaging features, such as disproportionately enlarged subarachnoid space hydrocephalus[3] and a small callosal angle (CA),[4,5] have been reported as characteristic features of iNPH. Ishii et al. initially defined the CA in the coronal plane at the posterior commissure (PC) that is perpendicular to the anterior commissure (AC)-PC line and demonstrated its classification efficacy in discriminating iNPH from Alzheimer's disease (AD) or healthy controls (HCs).[4] The CA in the coronal plane at the AC that is perpendicular to the AC-PC line has been reported to be a reliable marker for distinguishing iNPH from AD or HCs.[5] On the other hand, the splenium of the corpus callosum connects the bilateral parietal, temporal, and occipital lobes, which are involved in multiple functions such as spatial orientation and cognition.[6,7] Recently, the splenial angle, an axial angular index of lateral ventriculomegaly measured on diffusion tensor MRI color fractional anisotropy maps, has been useful for differentiating NPH from AD or Parkinson's disease (PD).[8] That report indicated that the splenium of the corpus callosum is associated with the pathophysiology of iNPH. However, unlike conventional MRI, diffusion MRI is not often used in a general clinical practice. There have been no studies using conventional MRI to evaluate CA in the axial plane at the genu or splenium of the corpus callosum in iNPH patients.

The Timed Up and Go (TUG) test is one of the representative tests to evaluate functional mobility and gait function in iNPH patients.[9] Japanese diagnostic guidelines for iNPH also include TUG as one of the tests for evaluating the response to a tap test or shunt operation. However, no studies have specified the neural correlates for a prolonged TUG test total time in patients with iNPH.

In this study, we aimed to evaluate the clinical usefulness of four CAs—in the axial plane at the splenium and the genu and in the coronal plane at the AC and the PC—in iNPH patients.

Methods

Participants

We included patients with a clinical diagnosis of iNPH, PD, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), AD, PD with dementia (PDD), or dementia with Lewy bodies (DLB) who had been admitted to the Departments of Neurology and Neurosurgery at Tokyo Medical and Dental University Hospital, Department of Neurology at the Kanto Central Hospital, or Department of Neurology at the Kamagaya General Hospital from 2010 to 2020. Clinical diagnosis was made according to the Japanese guidelines for clinically probable or definite iNPH;[10] Movement Disorder Society clinical diagnostic criteria for clinically probable or established PD;[11] Awaji diagnostic criteria for possible, probable, or definite ALS;[12] McDonald's criteria for MS;[13] National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for probable AD;[14] diagnostic criteria for probable PDD;[15] or diagnostic criteria for possible or probable DLB.[16] Exclusion criteria were the presence of other neurological diseases such as a brain tumor or stroke and no 3-dimensional T1-weighted (3DT1) MRI data. iNPH patients were further classified according to a shunt operation, TUG test total time and Mini-Mental State Examination (MMSE) total score after a shunt operation, and available 3DT1 MRI after a shunt operation. Patients with PD, ALS, or MS were classified as the control group for motor function, and those with AD, PDD, or DLB were classified as the control group for cognitive function. We also enrolled patients with hydrocephalus (Evans index[17] > 0.3) who did not respond to a tap test, regardless of their etiologies and comorbidities.

HCs were recruited from among friends and spouses of patients enrolled in the study. HCs were defined by a normal neurological physical assessment and normal cognitive function based on the Japanese version of the MMSE[18] or the Montreal Cognitive Assessment. HCs were evaluated with MRI as part of a prospective study to obtain normal brain imaging data. The subjects whose MRI demonstrated abnormal white matter high-intensity areas showing Fazekas grade 2 or 3 were excluded.[19]

For patients with iNPH or AD and hydrocephalus patients without a tap test response, a retrospective observational cohort study was performed, and extracted data were de-identified; written informed consent was waived for this portion of the study. Other data were collected as part of a prospective study, and written informed consent was obtained from patients with PD, ALS, MS, PDD, or DLB or from HCs. This study was approved by the institutional review boards of Tokyo Medical and Dental University Hospital, Kanto Central Hospital, and Kamagaya General Hospital, and we were allowed to analyze data that had been collected retrospectively or prospectively cojointly as a multiinstitutional study.

Clinical and Radiological Assessments

All iNPH patients were evaluated with the TUG test and MMSE. All subjects in the control group for motor function were also evaluated with the TUG test. The TUG test was performed using a standardized method.[20] All patients and HCs were instructed to walk at a safe, fast-paced gait to minimize intersubject variation. Participants performed the TUG test 3 times, and the mean TUG total time was used for analysis. While the TUG test was performed in three hospitals, one author (T.H.) worked in all three hospitals and instructed the clinical staff in performing identical tests. All subjects in the control group for cognitive function were evaluated with the MMSE.

All enrolled subjects were evaluated with 3DT1 MRI using the 1.5- or 3-T brain scanner at each hospital.

Image Acquisition

For patients at the Tokyo Medical and Dental University Hospital, 3DT1 images were obtained using magnetization-prepared rapid acquisition with gradient echo (MPRAGE) sequences on a 3.0-T MRI scanner (MAGNETOM Spectra, Siemens Healthcare; TR = 1800 msec, TE = 2.42 msec, TI = 900 msec, flip angle = 9°, FOV = 250 × 250 mm, matrix = 256 × 256, 1-mm sagittal slices, number of slices = 192, total acquisition time =

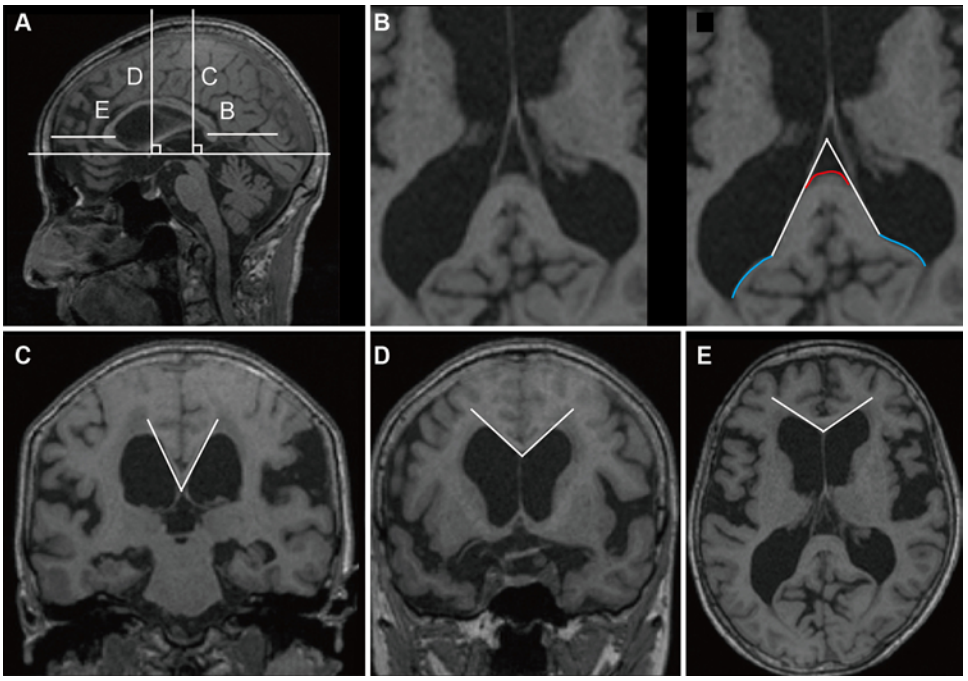

FIG. 1. Four planes were used to measure CAs (**A**). The CA at the splenium (**B**) is measured in the axial plane parallel to the AC-PC line at the center of the splenium. Axial image of the splenium consists of three areas: tip area (*red*), straight areas, and outermost areas (*blue*). *White lines* are extended from the straight areas. The CA at the splenium is measured at the crossing point. The CA in the coronal plane at the AC (**D**) or the PC (**C**) was measured in the coronal plane that is perpendicular to the AC-PC line. The CA at the genu (**E**) is measured in the axial plane that is parallel to the AC-PC line at the center of the genu. Figure is available in color online only.

4 minutes 10 seconds). For patients at the Kanto Central Hospital, 3DT1 images were obtained using MPRAGE sequences on a 1.5-T MRI scanner (Symphony, Siemens; TR = 2150 msec, TE = 3.93 msec, TI = 1100 msec, flip angle = 15°, FOV = 230 × 230 mm, matrix = 256 × 256, 1-mm sagittal slices, number of slices = 160, total acquisition time = 5 minutes 3 seconds). For patients at the Kamagaya General Hospital, 3DT1 images were obtained using spoiled gradient echo sequences on a 1.5-T scanner (Signa Excite, GE Healthcare; TR = 5436 msec, TE = 1.34 msec, TI = 0 msec, flip angle = 20°, FOV = 220 mm, matrix = 256 × 256, 1.5-mm sagittal slices, number of slices = 116, total acquisition time = 5 minutes 37 seconds).

Measurement of Four CAs

The CA was measured in the axial planes at the splenium (Fig. 1B) and the genu (Fig. 1E) that are parallel to the AC-PC line by using ImageJ.[21] The splenium of the corpus callosum is separated by three areas: tip area, straight areas, and outermost areas. The CA at the splenium was measured at the crossing point (Fig. 1B). The CA in the coronal planes at the AC (Fig. 1D) and the PC (Fig. 1C) that are perpendicular to the AC-PC line was measured according to previous reports.[4,5] Measurements of the CA were conducted independently by two neurologists (T.H. and M.O.) who were blinded to clinical information.

Other Parameters of Hydrocephalus

As other parameters of hydrocephalus, the Evans index,[17] frontal-occipital horn ratio,[22] and third ventricular width[23] were measured in iNPH patients.

Probabilistic Tractography Analysis

Data used in this part of the study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography, other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of mild cognitive impairment and early AD. We used diffusion tensor imaging data (3.0-T MRI, Siemens; 54 gradient directions, 2-mm isovoxel) collected from 11 HCs (mean age 60.8 ± 3.2 years, 8 females) for probabilistic tractography analysis with FMRIB's Diffusion Toolbox (www.fmrib.ox.ac.uk/fsl). A seed mask for the splenium of the corpus callosum was defined by the sagittal slice (Montreal Neurological Institute coordinate, x = 90) defined by the ICBM-DTI-81 white-matter labels atlas. Probabilistic fiber tracking was initiated from all voxels within the seed mask to generate 5000 streamline samples with a curvature threshold of 0.2. The generated tractography was spatially normalized and averaged over 11 subjects.

Statistical Analysis

Statistical analyses were performed using Prism 8 or 9

TABLE 1. Demographic and clinical data of enrolled subjects

Variable	iNPH	Control Groups for Motor Function				Control Groups for Cognitive Function				Intergroup Difference Btwn iNPH & Control Groups
		PD	ALS	MS	HC	AD	PDD	DLB	HC	
Identifier for group comparisons	A	B	C	D	E	F	G	H	I	
No. of subjects	40	26	18	23	20	113	28	33	30	
Age in yrs	78.0 (5.1)	69.2 (8.4)	68.9 (8.7)	47.2 (7.2)	68.2 (5.1)	80.7 (5.7)	79.4 (4.5)	79.7 (5.5)	77.7 (4.5)	A>B–E*, A<F†
Sex: M/F	25/15	13/13	8/10	4/19	10/10	27/86	15/13	18/15	15/15	A>D, F*
Disease duration in yrs	2.3 (2.1)	1.7 (1.5)	1.9 (1.5)	10.2 (7.7)	—	2.5 (2.0)	5.7 (4.1)	2.6 (2.8)	—	A<D, G*
TUG total time in sec	16.2 (5.1)	8.2 (1.5)	8.3 (2.0)	7.5 (1.5)	6.0 (0.8)	—	—	—	—	A>B–E*
MMSE total score	22.2 (4.3)	—	—	—	—	20.2 (3.9)	20.6 (3.6)	20.0 (6.9)	29.1 (0.7)	A>F, H‡, A<I*

Data are expressed as the mean (standard deviation), unless indicated otherwise.
* $p < 0.001$.
† $p < 0.01$.
‡ $p < 0.05$.

software (GraphPad Software) and SAS version 9.4 software (SAS Institute Inc.). Intergroup differences between patients with iNPH and other control groups were evaluated using the Student t-test for parametric variables or the Mann-Whitney U-test for nonparametric variables. The normality of the data was evaluated with the Shapiro-Wilk test.

For intergroup differences between patients with iNPH and others, multiple comparisons were corrected with the false discovery rate using the Benjamini-Krieger-Yekutieli method. Regarding the comparison of CAs between iNPH and other groups, ANCOVA was performed with defining age as a covariate.

The primary outcome measure was defined as the correlation between CAs and TUG test total time or MMSE total score in iNPH patients. For iNPH patients who underwent a shunt operation, TUG test and MMSE results were evaluated at a follow-up visit. The correlation was evaluated using Pearson's correlation coefficient for parametric data or Spearman's rank correlation coefficient for nonparametric data. The multiple comparison was corrected by the Bonferroni method. Correlations between three other hydrocephalus parameters and TUG total time or MMSE total score were evaluated in iNPH patients as secondary outcome measures. The correlations in control groups were secondary outcome measures.

Multiple linear regression analysis with the forced entry method was applied for the CAs that were significantly correlated in the correlation analysis. The TUG total time or MMSE total score was treated as the dependent variable, CA was considered an independent variable, and age, sex, and disease duration were the covariate variables. Multiple collinearity among independent variables and covariates was evaluated using the variance inflation factor (VIF).

Receiver operating characteristic (ROC) curve analysis was performed to distinguish iNPH patients from control subjects. For each model, we calculated the area under the curve with optimism correction using the internal bootstrap method,[24] along with its 95% confidence interval. The bootstrap was replicated 1000 times. We selected the cutoff values for CA using the maximum Youden's index.

Mean values are expressed with standard deviations. The criterion for statistical significance was $p < 0.05$.

Results

Patient Demographics

A total of 40 patients with iNPH who had 3DT1 MRI data were ultimately enrolled in this study. Twenty-three of these 40 patients underwent a shunt operation (Supplementary Fig. 1). Moreover, 26 patients with drug-naïve PD, 18 with ALS, 23 with MS, 113 with AD, 28 with PDD, 33 with DLB, and 50 HCs were also enrolled (Table 1).

Fourteen hydrocephalus patients who did not have a tap test response (mean age 70.9 ± 8.3 years, 5 females) were also enrolled. These patients consisted of 2 with late-onset idiopathic aqueductal stenosis, 1 with Dandy-Walker syndrome, 4 with AD, 1 with vascular parkinsonism, and 6 with unknown etiologies. Among this group, the mean TUG test total time, MMSE total score, and CA at the splenium were 10.5 ± 3.2 seconds, 25.5 ± 4.3, and 70.2° ± 23.9°, respectively.

Correlation Analysis for CAs in iNPH Patients and Control Groups

The intraclass correlation coefficients for interexaminer reliability in evaluating CAs were as follows: at the splenium 0.86, 95% CI 0.64–0.95; in the AC plane 0.98, 95% CI 0.94–0.99; in the PC plane 0.96, 95% CI 0.90–0.99; and at the genu 0.88, 95% CI 0.68–0.96.

MRI features in patients and HCs are shown in Table 2. CAs in the axial plane at the splenium and in the coronal plane at the PC or AC were significantly smaller in patients with iNPH than in any subjects in the control groups.

The correlation between CA and TUG total time or MMSE total score is summarized in Table 3. Only CA at the splenium in patients with iNPH was significantly cor-

related with TUG total time (Spearman's rank correlation coefficient r = −0.612, p < 0.001) or MMSE total score (Pearson correlation coefficient r = 0.415, p = 0.008; Fig. 2). The Frontal Assessment Battery (FAB) was used in 27 of the 40 patients with iNPH. There was no correlation between CA at the splenium and FAB (Spearman's rank correlation coefficient r = 0.088, p = 0.662). In all control groups, TUG total time or MMSE total time was not correlated with CA in any planes (Table 3).

In the hydrocephalus group without a tap test response, CA at the splenium was not correlated with TUG total time (Spearman's rank correlation coefficient r = 0.143, p = 0.627) or MMSE total score (Spearman's rank correlation coefficient r = −0.033, p = 0.911) (Supplementary Fig. 2).

In multiple regression analyses corrected for age, sex, and disease duration, the TUG total time was predicted by age (95% CI 0.198–0.748, p = 0.001) and CA at the splenium (95% CI −0.270 to −0.040, p = 0.010) and the MMSE total score was predicted by CA at the splenium (95% CI 0.034–0.288, p = 0.014) in patients with iNPH. All variables included in the model had a VIF < 2.

Scatterplots depicting the relationship between three parameters for hydrocephalus and TUG total time or MMSE total score are shown in Supplementary Fig. 3. The mean Evans index, frontal-occipital horn ratio, and third ventricular width were 0.34 ± 0.04, 0.61 ± 0.07, and 13.4 ± 2.3 mm, respectively. There were no significant associations between the three parameters for hydrocephalus and TUG total time or MMSE total score in iNPH patients.

Classification Efficacy of Four CAs for iNPH

ROC curve analysis showed that CA at the splenium as well as in the coronal plane at the PC successfully distinguishes patients with iNPH from other neurological diseases and HCs (Table 4). The cutoff value for CA at the splenium was 71.1° and had a sensitivity of 90.0% and a specificity of 89.0%, and the maximum Youden's index was 0.79.

Change of CA in Four Different Planes in Response to the Shunt Operation

The CA at the splenium was enlarged after the shunt operation (62.3° ± 15.0° before vs 71.6° ± 17.4° after, p = 0.001; Fig. 3A), as was CA in the coronal plane at the PC (64.6° ± 18.2° vs 80.9° ± 27.5°, respectively, p = 0.003) and CA at the AC (107.6° ± 15.7° vs 115.2° ± 16.2°, respectively, p = 0.012), but CA at the genu (112.6° ± 10.6° vs 115.5° ± 10.2°, respectively, p = 0.059) was not statistically significantly altered after the shunt operation.

The CA at the splenium of a representative patient with iNPH before and after the shunt operation are shown in Fig. 3B and 3C. Gait disturbance in this patient improved after the shunt operation (TUG total time 17.6 before vs 10.5 seconds after). In iNPH patients who underwent a shunt operation, the CA at the splenium tended to be associated with TUG total time (Fig. 3D) or MMSE total score (Fig. 3F) before the shunt operation, but these tendencies diminished after the shunt operation (Fig. 3E and 3G).

TABLE 2. CAs at four different planes

Variable	iNPH	Control Groups for Motor Function					ANCOVA, p Value	Post Hoc SGNFC	Control Groups for Cognitive Function				ANCOVA, p Value	Post Hoc SGNFC
		PD	ALS	MS	HC				AD	PDD	DLB	HC		
Identifier for group comparisons	A	B	C	D	E				F	G	H	I		
No. of subjects	40	26	18	23	20				113	28	33	30		
CA in axial plane at splenium	59.1 (12.3)	92.4 (15.7)	82 (15.9)	95.1 (10.6)	95.0 (12.4)	<0.001*	A<B–E*		84.8 (13.2)	78.7 (12.3)	80.2 (11.8)	93.2 (12.5)	<0.001*	A<F–I*
CA in coronal plane at PC	64.2 (17.3)	108.9 (12.7)	105.0 (20.2)	118.9 (10.1)	115.8 (13.3)	<0.001*	A<B–E*		105.4 (15.4)	99.4 (17.9)	102.3 (18.1)	111.2 (9.4)	<0.001*	A<F–I*
CA in coronal plane at AC	105.4 (18.7)	128.9 (7.2)	128.3 (8.9)	134.1 (7.4)	130.2 (7.5)	<0.001*	A<B–E*		127.2 (8.5)	124.7 (9.6)	126.0 (10.5)	128.0 (6.2)	<0.001*	A<F–I*
CA in axial plane at genu	107.3 (9.8)	112.5 (7.4)	107.0 (4.7)	109.8 (9.8)	111.6 (6.4)	0.036†	—		113.3 (8.8)	114.9 (8.5)	112.2 (7.8)	111.1 (5.8)	0.005‡	A<F*, A<G‡

SGNFC = significance.
Data are expressed as the mean (standard deviation), unless indicated otherwise. ANCOVA was performed treating age as a covariate with Dunnett's correction for the iNPH group and control groups for motor function or cognitive function.
* p < 0.001.
† p < 0.05.
‡ p < 0.01.

TABLE 3. Correlation between CAs and TUG total time or MMSE total score

Correlation Btwn CA & TUG Test Total Time										
	iNPH (n = 40)		PD (n = 26)		ALS (n = 18)		MS (n = 23)		HC (n = 20)	
CA	r	p Value	r	p Value	r	p Value	r	p Value	r	p Value
At splenium	−0.612	**<0.001**	−0.069	0.736	−0.212	0.398	0.016	0.944	0.293	0.210
In coronal plane at PC	−0.193	0.232	−0.348	0.082	−0.051	0.842	−0.419	0.047	0.212	0.370
In coronal plane at AC	−0.095	0.559	−0.102	0.619	−0.095	0.708	0.251	0.249	0.063	0.792
At genu	−0.097	0.553	−0.217	0.287	−0.047	0.853	0.251	0.248	0.545	0.013
Correlation Btwn CA & MMSE Total Score										
	iNPH (n = 40)		AD (n = 113)		PDD (n = 28)		DLB (n = 33)		HC (n = 30)	
CA	r	p Value	r	p Value	r	p Value	r	p Value	r	p Value
At splenium	0.415	**0.008**	0.088	0.352	0.391	0.040	0.043	0.810	0.121	0.524
In coronal plane at PC	0.149	0.359	−0.038	0.691	0.280	0.149	−0.074	0.682	0.333	0.072
In coronal plane at AC	0.145	0.371	0.041	0.665	−0.269	0.166	−0.191	0.288	0.043	0.821
At genu	−0.059	0.718	0.046	0.628	0.083	0.673	−0.308	0.081	0.036	0.851

Data are presented as the mean (standard deviation), unless indicated otherwise. Significance was set at $p < 0.0125$, indicated by boldface type.

Fiber Projection From the Splenium of the Corpus Callosum

Probabilistic tractography analysis showed that neuronal fibers passing through the seed mask of the splenium of the corpus callosum (Fig. 4A) connect the bilateral parietal lobes, especially the superior parietal lobules, temporal lobes, and occipital lobes (Fig. 4B). The number of averaged streamlines was thresholded by 100 and is shown by color in the figure.

Discussion

This study demonstrated that CA at the splenium is correlated with TUG test total time and MMSE total score in patients with iNPH, but not in any of the control groups. The associations between CA at the splenium and TUG total time or MMSE total score tended to deteriorate after a shunt operation. Other parameters of hydrocephalus—Evans index,[17] frontal-occipital horn ratio,[22] and third ventricular width[23]—were not correlated with TUG total time or MMSE total score in patients with iNPH. Thus, CA at the splenium is a unique morphological feature that correlates with gait and cognition in iNPH patients.

This study also indicated that CA at the splenium has high classification efficacy in differentiating iNPH from other neurological diseases and HCs.

Mechanism of a Small CA

The pathogenesis of a small CA is proposed as follows: the roof of the lateral ventricle is forced to elevate by the mechanical pressure from the enlarged lateral ventricles, whereas the corpus callosum is anchored to the floor of the lateral ventricle via the fornix and the septum pellucidum, and the corpus callosum cannot be elevated, unlike other parts of the roof, resulting in a smaller CA in iNPH.[2] Therefore, a small CA indicates the presence of abnormal mechanical pressure over the corpus callosum, and the deformed corpus callosum may reflect the damaged interhemispheric fibers. It is known that CA at the PC increases after shunt surgery in iNPH patients.[25] This study is the first to demonstrate that CA at the splenium also increases after shunt surgery, presumably reflecting decompression of the enlarged lateral ventricle.

Tractography Analysis From the Splenium of the Corpus Callosum

The probabilistic tractography analysis demonstrated that neural fibers from the splenium of the corpus callosum connect to the bilateral parietal, temporal, and occipital lobes (Fig. 4B). Herein, iNPH patients exhibited a small CA at the splenium (Table 2), which suggests that interhemispheric fibers via the splenium of the corpus callosum were damaged in iNPH patients. Among the projected fibers to the parietal lobes, most terminated in the superior parietal lobules (Fig. 4B). The superior parietal lobules are engaged in multiple functions such as visuospatial attention,[26] mental rotation,[27] and sensorimotor integration.[28] Patients with a lesion of the superior parietal lobules have difficulty with visually guided movements.[29] Patients with lesions in the bilateral superior parietal lobules have global spatial disorientation probably because of a visuomotor intrahemispheric disconnection.[30] The splenium of the corpus callosum also contains the forceps major, which consists of thick interhemispheric bundles connecting the bilateral occipital lobes. Patients with a unilateral lesion in the forceps major have topographical disorientation and impaired manipulation of visuospatial information.[31] Therefore, a small CA at the splenium may indicate the presence of multiple splenium-related dysfunctions.

Neural Correlates of Gait Disturbance in iNPH

The TUG test consists of four subtasks: sit to stand, stand to sit, walking, and turning.[32] In particular, sit to

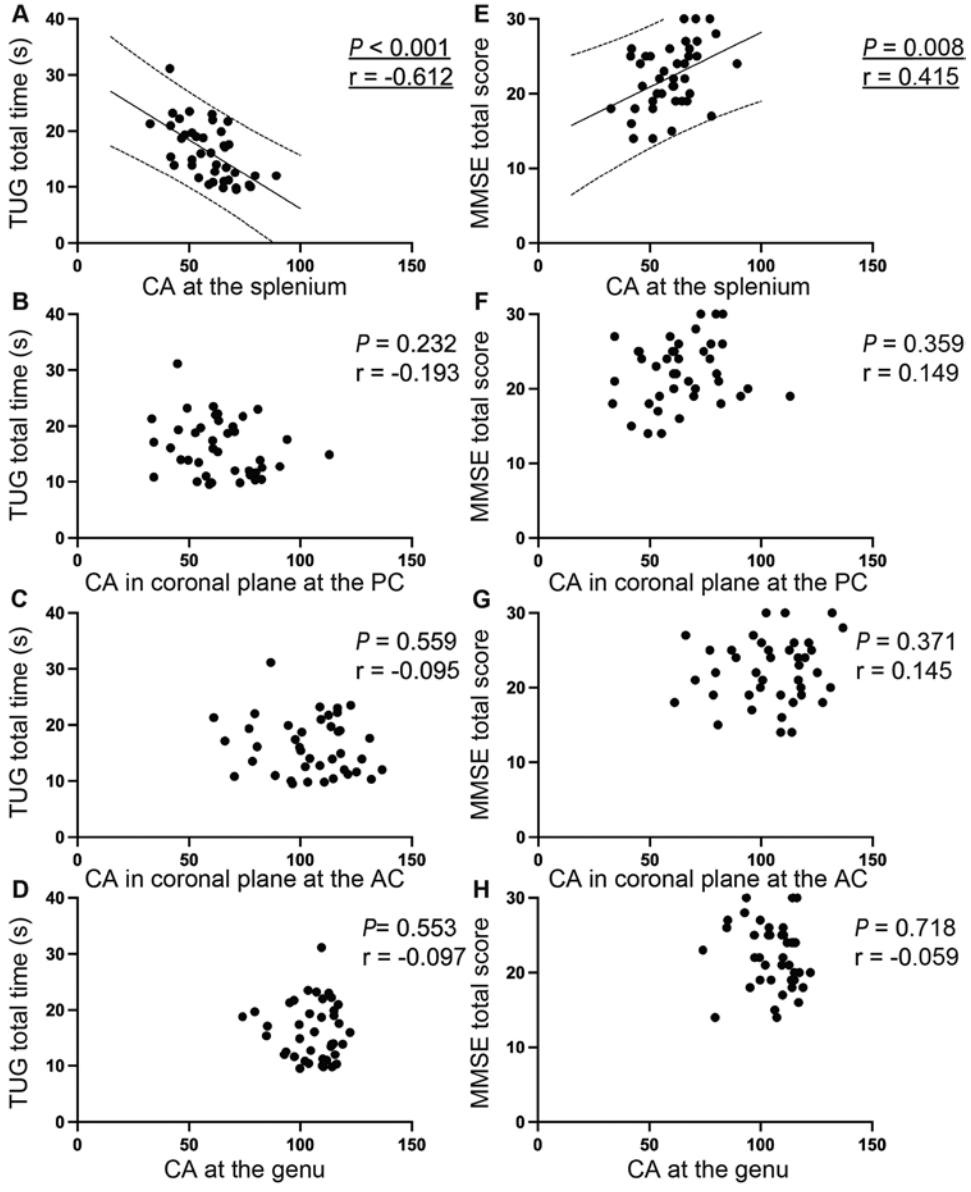

FIG. 2. Scatterplots for CA at the splenium (**A and E**), in the coronal plane at the PC (**B and F**), in the coronal plane at the AC (**C and G**), and at the genu (**D and H**) against TUG total time or MMSE total score in patients with iNPH, respectively. Only CA at the splenium was significantly correlated with TUG total time or MMSE total score. The regression line and 95% prediction interval are also shown.

stand, stand to sit, and turning are visually guided movements that require sensorimotor integration and spatial orientation. We speculate that disrupted interhemispheric connections between the bilateral superior parietal lobules and the occipital lobes cause impaired visuospatial attention, sensorimotor integration, spatial orientation, and manipulation of visuospatial information, resulting in a prolonged TUG total time in iNPH patients.

While neural correlates for gait disturbance remain to be specified in iNPH, several clinical radiological associations have been reported: for example, CA in the coronal plane at the PC and the balance scale;[33] CA in the coronal plane at the AC and iNPH grading scale total score or Tinetti gait score;[34] fractional anisotropy values in the corpus callosum and gait disturbance on the iNPH grading scale;[35] fractional anisotropy values in the left anterior limb of the internal capsule or under the left supplementary motor area and number of steps in the TUG test;[36] and mean diffusivity in the corticospinal tract and gait disturbances.[37] Patients with iNPH exhibit several forms of gait disturbance such as impaired balance, magnetic gait, apraxia of gait, freezing of gait, slowness of gait, and/or impaired turning.[1] Thus, complex pathogeneses underlie the multifaceted gait disturbance in iNPH. We propose that the splenium of the corpus callosum is one of the neural substrates of gait disturbance in iNPH patients.

TABLE 4. ROC curve analysis for CAs to distinguish patients with iNPH from those with other neurological diseases or HCs

Variable	Cutoff Value of Measure	Sensitivity (%)	Specificity (%)	AUC (95% CI)	Optimism Corrected AUC (95% CI)
CA at splenium					
Compared w/ PD, ALS, MS	71.1	90.0	91.0	0.948 (0.935–0.962)	0.949 (0.936–0.963)
Compared w/ AD, PDD, DLB	71.1	90.0	86.2	0.913 (0.896–0.931)	0.912 (0.895–0.931)
Compared w/ HCs	71.1	90.0	96.0	0.977 (0.970–0.986)	0.976 (0.970–0.986)
Compared w/ all control subjects	71.1	90.0	89.0	0.932 (0.920–0.945)	0.931 (0.920–0.945)
CA in coronal plane at PC					
Compared w/ PD, ALS, MS	82.9	92.5	95.5	0.960 (0.947–0.975)	0.961 (0.948–0.975)
Compared w/ AD, PDD, DLB	82.9	92.5	88.5	0.943 (0.931–0.959)	0.942 (0.930–0.958)
Compared w/ HCs	90.9	95.0	100.0	0.988 (0.978–0.992)	0.990 (0.981–0.995)
Compared w/ all control subjects	82.9	92.5	92.1	0.955 (0.944–0.967)	0.955 (0.944–0.967)
CA in coronal plane at AC					
Compared w/ PD, ALS, MS	122.6	82.5	89.6	0.914 (0.894–0.935)	0.914 (0.894–0.935)
Compared w/ AD, PDD, DLB	118.1	77.5	83.9	0.858 (0.834–0.885)	0.857 (0.834–0.884)
Compared w/ HCs	118.1	77.5	92.0	0.901 (0.880–0.925)	0.901 (0.880–0.925)
Compared w/ all control subjects	118.1	77.5	87.3	0.878 (0.858–0.901)	0.878 (0.858–0.901)
CA at genu					
Compared w/ PD, ALS, MS	99.9	25.0	92.5	0.560 (0.530–0.600)	0.546 (0.517–0.586)
Compared w/ AD, PDD, DLB	117.0	92.5	38.5	0.671 (0.641–0.702)	0.671 (0.641–0.702)
Compared w/ HCs	99.9	25.0	98.0	0.606 (0.567–0.646)	0.602 (0.564–0.642)
Compared w/ all control subjects	117.0	92.5	30.6	0.634 (0.605–0.662)	0.635 (0.605–0.662)

AUC = area under the curve.

Neural Correlates of Cognitive Impairment in iNPH

The neural underpinnings of cognitive impairment also remain to be identified in iNPH. The temporal lobes are related to memory, semantics, and language processing. The splenium of the corpus callosum contains the interhemispheric fibers connecting the bilateral temporal lobes. Herein, FAB total scores were not correlated with CA at the splenium. This may be explained by the fact that the splenium of the corpus callosum does not contain the interhemispheric fibers from the frontal lobes. On the other hand, there is diffuse white matter damage in iNPH,[38] and this diffuse damage may be responsible for the multifaceted cognitive impairment in iNPH. The MMSE consists of several subtests that are based on functions of the temporal, parietal, and occipital lobes.[39] We speculate that disrupted interhemispheric connections between the bilateral parietal, temporal, and occipital lobes are relevant to lower MMSE total scores in iNPH patients. We propose that the splenium of the corpus callosum is one of the critical neural correlates of cognitive impairment in iNPH.

Posterior-Dominant Damage of the Corpus Callosum in iNPH

In this study, ROC analysis showed that CA at the splenium or in the coronal plane at the PC had higher sensitivity and specificity in discriminating iNPH from other neurological diseases and HCs, as compared to CA at the genu or in the coronal plane at the AC. This result is consistent with a prior report.[40] Previously, Hattori et al. showed that fractional anisotropy values are significantly decreased in the splenium and posterior body of the corpus callosum in patients with iNPH compared with those in HCs, but that those in the genu or anterior body of the corpus callosum are not different.[38] As fractional anisotropy values in the corticospinal tract in iNPH are increased because of the enlarged lateral ventricle, the compressed white matter tends to have higher fractional anisotropy values.[41] While the corpus callosum is compressed in iNPH, the splenium and posterior body of the corpus callosum have decreased fractional anisotropy values, suggesting the presence of intense damage in the posterior parts of the corpus callosum in iNPH. Taken together, there is structural vulnerability in the posterior part of the corpus callosum in iNPH.[8] The posterior-dominant damage of the corpus callosum gives us more evidence to propose that CA at the splenium reflects gait and cognitive disturbances in iNPH.

Study Limitations

The current study has several limitations. First, only a limited number of patients with iNPH underwent a shunt operation in this study. Second, the intraclass correlation coefficient for interexaminer reliability in evaluating CA at the splenium was lower than those in evaluating CA at the AC plane or the PC plane. This is probably due to the thick and complex three-dimensional structure of the splenium of the corpus callosum, leaving more space for

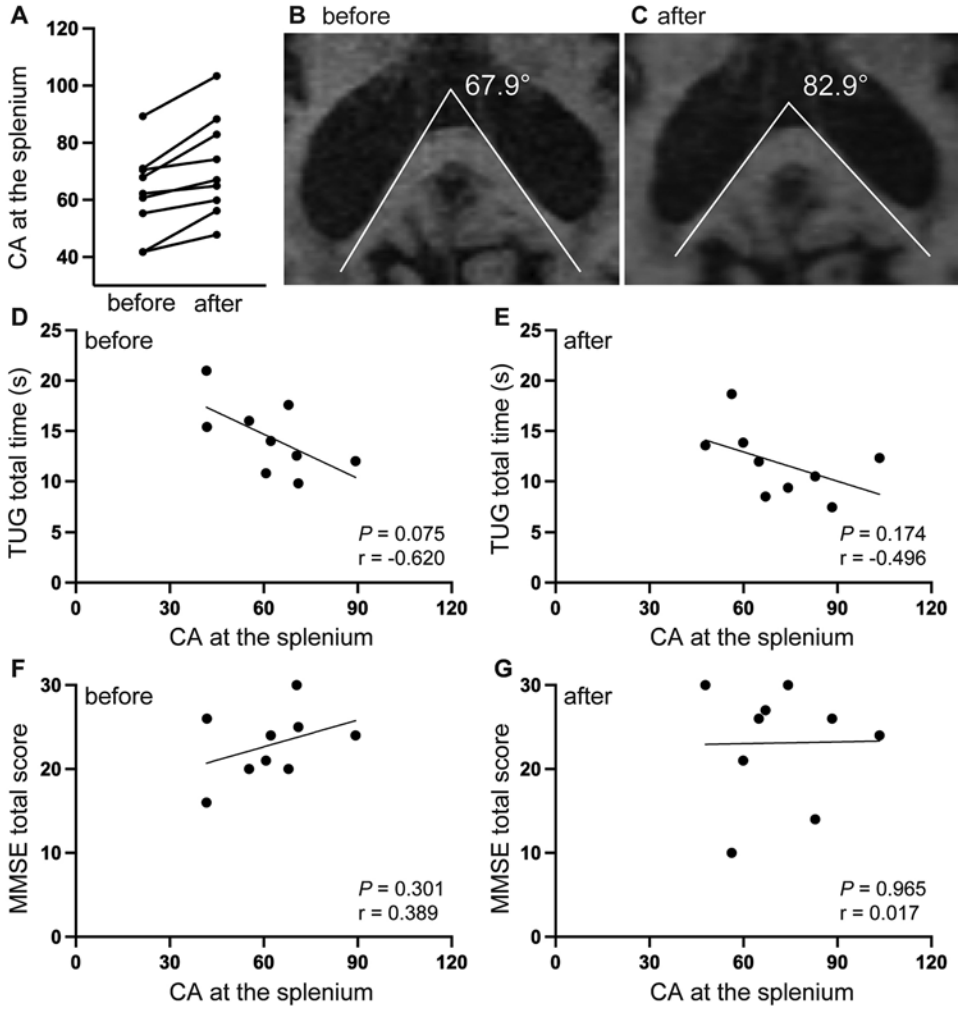

FIG. 3. All CAs at the splenium were enlarged after the shunt operation (**A**). Representative case for CA at the splenium before (**B**) and after (**C**) the shunt operation. This patient had remarkable improvement in gait disturbance after the shunt operation (TUG total time 17.6 before vs 10.5 seconds after). CA at the splenium tended to correlate with TUG total time or MMSE total score before the shunt operation (**D and F**) but correlated less or not all after the shunt operation (**E and G**).

interrater variability. Third, we did not evaluate amyloid-β and tau proteins in the cerebrospinal fluid, nor did we perform dopamine transporter imaging in most of the iNPH patients. Some patients with iNPH may develop other neurodegenerative disorders in the later stages of their disease. Fourth, we did not evaluate the intergroup difference of structural connectivity between the bilateral parietal, temporal, and occipital lobes in patients with iNPH and those in HCs by using probabilistic tractography. Finally, we did not evaluate more detailed cognitive tests other than the MMSE or FAB to assess which cognitive domain was associated with CA at the splenium.

Conclusions

We propose that CA at the splenium correlates with gait and cognition in iNPH. The mechanical compression at the splenium of the corpus callosum may cause the interhemispheric disconnections among the parietal (especially the superior parietal lobules), temporal, and occipital lobes, resulting in gait and cognitive impairments in iNPH patients.

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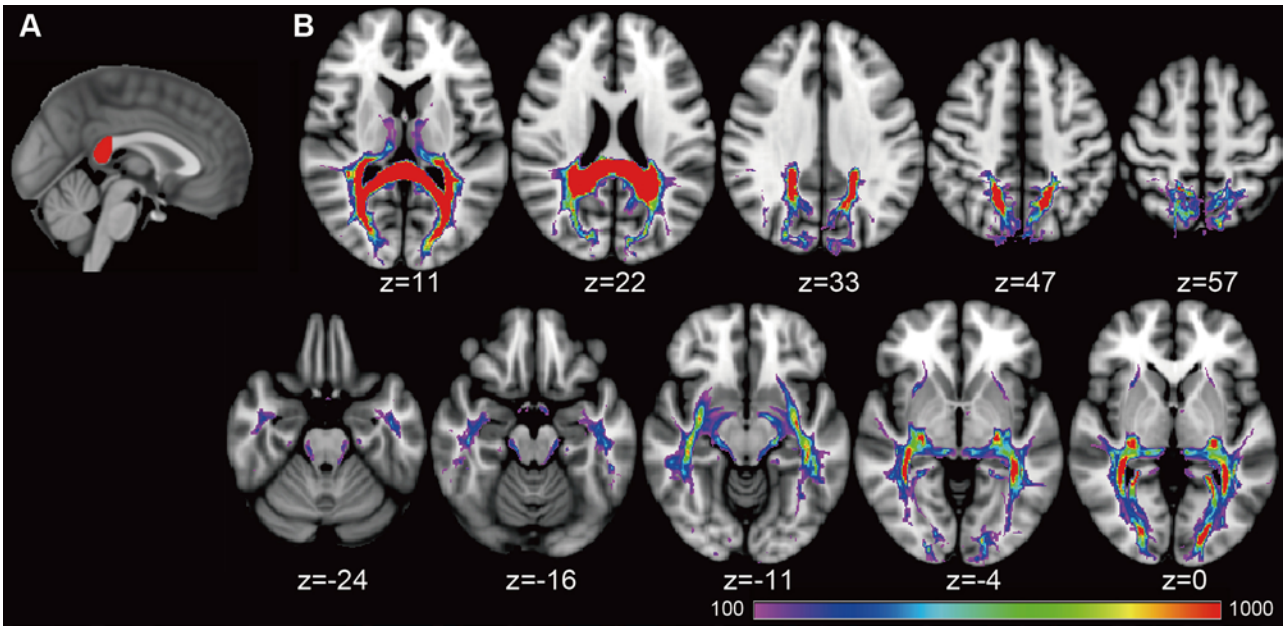

FIG. 4. A: A seed mask for the splenium of the corpus callosum was defined using the sagittal slice of ICBM-DTI-81 white-matter labels atlas. **B:** Averaged probabilistic tractography shows that neural fibers from the splenium project to the bilateral parietal lobes, especially the superior parietal lobules and the temporal and occipital lobes. Averaged numbers of trajectories are shown by color. Figure is available in color online only.

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Dr. Hattori reported personal fees from Daiichi Sankyo Co., Sumitomo Dainippon Pharma Co. Ltd., Integra Japan Co. Ltd., and Kyowa Kirin Co. Ltd. for speaker's honoraria outside the submitted work. Dr. Yokota reported collaborating with Daiichi Sankyo Co. Ltd., Mitsubishi Tanabe Pharma Corp., NanoCarrier Co. Ltd., Ono Pharmaceutical Co. Ltd., Rena Therapeutics Inc., Takeda Pharmaceutical Co. Ltd., Toray Industries Inc., and Ionis Pharmaceuticals. Dr. Yokota also serves as an academic adviser for Rena Therapeutics Inc. and has received speaker's honoraria from Kyowa Kirin Co. Ltd., Soyaku Yakuri Forum, Tokyo University of Science, Teijin Pharma Ltd., Takeda Pharmaceutical Company Ltd., Mitsubishi Tanabe Pharma Corp., Daiichi Sankyo Company Ltd., Nihon Mede-Physics Co. Ltd., Otsuka Pharmaceutical Co. Ltd., CSL Behring K.K., The Academy of Pharmaceutical Science and Technology, Japan, Kyoto Prefectural University of Medicine, Kawasaki Institute of Industrial Promotion, Nikkei Business Publications Inc., Astellas Pharma Inc., Biogen Japan Ltd., and Tokyo Medical Science.

Author Contributions

Conception and design: Hattori. Acquisition of data: Hattori, Ohara, Yuasa, Azuma, Chen, Orimo. Analysis and interpretation of data: Hattori, Ohara, Chen. Drafting the article: Hattori, Ohara, Chen. Critically revising the article: Hattori, Ohara, Azuma. Reviewed submitted version of manuscript: Hattori, Ohara, Hanazawa. Approved the final version of the manuscript on behalf of all authors: Hattori. Statistical analysis: Hattori, Ohara, Hanazawa, Hirakawa. Administrative/technical/material support: Hattori. Study supervision: Hattori, Yokota.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplementary Figs. 1–3. https://thejns.org/doi/suppl/10.3171/2022.12.JNS221825.

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