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Microstructural changes of the corticospinal tract in idiopathic normal pressure hydrocephalus: a comparison of diffusion tensor and diffusional kurtosis imaging

Atsushi Nakanishi · Issei Fukunaga · Masaaki Hori · Yoshitaka Masutani · Hattori Takaaki · Masakazu Miyajima · Shigeki Aoki

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Abstract
Introduction The goals of this study were to examine the usefulness of diffusional kurtosis imaging (DKI) for assessing microstructural changes in the compressed corticospinal tract (CST) among patients with idiopathic normal pressure hydrocephalus (iNPH).
Methods Eleven patients with iNPH (mean age: 73.6 years, range: 65–84), who underwent 3-T magnetic resonance imaging, including DKI before surgery, were recruited. Six age-matched, healthy subjects (mean age: 69.8 years, range: 60–75) served as the control group. DKI and diffusion tensor imaging parameters were calculated and compared between the iNPH and the control groups using tract-specific analysis of the CST at the level of the lateral ventricle.
Results Mean diffusional kurtosis (DK) and axial diffusion kurtosis were significantly lower in iNPH patients. However, apparent diffusion coefficient, fractional anisotropy, and axial eigenvalue (λ_1) were significantly higher in the iNPH group than in the control group.
Conclusions The mechanical pressure caused by ventricular enlargement in iNPH patients might induce formation of well-aligned fiber tracts and increased fiber density in the CST, resulting in decreased DK. DKI is able to depict both the altered microstructure and water molecule movement within neural axons and intra- or extracellular space. In addition, the investigated DKI parameters provide different information about white matter relative to conventional diffusional metrics for iNPH.

Keywords Diffusional kurtosis imaging · Idiopathic normal pressure hydrocephalus · Diffusion tensor imaging · Diffusional kurtosis metrics

Dr. Nakanishi and Mr Fukunaga contributed equally to this study.

A. Nakanishi (✉) · I. Fukunaga · M. Hori · S. Aoki
Department of Radiology, School of Medicine, Juntendo University, 2-1-1 Hongo,
Bunkyo-ku, Tokyo 113-8421, Japan
e-mail: naka24@juntendo.ac.jp

I. Fukunaga
Department of Health Science, Graduate School of Human Health Sciences, Tokyo Metropolitan University, 7-2-10, Higashiogu,
Arakawa, Tokyo 116-8551, Japan

Y. Masutani
Division of Radiology and Biomedical Engineering, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo,
Bunkyo-ku, Tokyo 113-8655, Japan

H. Takaaki
Department of Neurology and Neurological Science, Graduate School, Tokyo Medical and Dental University, 1-5-45 Yushima,
Bunkyo-ku, Tokyo 113-8510, Japan

M. Miyajima
Department of Neurosurgery, School of Medicine, Juntendo University, 2-1-1 Hongo,
Bunkyo-ku, Tokyo 113-8421, Japan

Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is a condition that is clinically characterized by a triad of symptoms: gait disturbance, cognitive deterioration, and urinary incontinence. It is also associated with ventricular enlargement in the absence of elevated cerebrospinal fluid (CSF) pressure [1, 2]. This ventricular enlargement has been hypothesized to be caused by

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reduced CSF absorption by the arachnoid villi or capillaries [3, 4].

Previous studies have shown that mechanical compression of neural tracts, caused by the enlargement of the lateral ventricles, is responsible for the characteristic gait disturbances [2–4], the most frequent and treatable symptom associated with iNPH [5]. Gait disturbance is treated by CSF shunting, which results in significant improvements for the majority of appropriately evaluated patients. Although the etiology of gait disturbance is not completely clear, various hypotheses have been proposed, including possible distortion of the corticospinal tract (CST) [6]. The CST, which connects the motor cortex and the spinal cord, runs along the side of the lateral ventricle and is presumably deformed by ventricular enlargement. It is not complicated to depict the CST tractography using diffusion tensor imaging (DTI). Hence, we hypothesized that the microstructure of the CST in iNPH patients is altered by mechanical pressure resulting from ventricular enlargement. Previous studies have examined the diffusion tensor metrics of iNPH, including increased fractional anisotropy (FA) of the CST, using the region of interest (ROI)-based, voxel-based [7], and tract-specific analysis [8]. Those studies suggested that chronic ventricular dilatation could change the microstructure of the CST in iNPH patients. However, the details of these microstructural changes remain unknown.

Diffusional kurtosis imaging (DKI) is a new technique that is based on non-Gaussian water diffusion analysis. Because water diffusion in the brain is restricted (non-Gaussian), DKI can provide additional information derived from the tissue microstructure, as compared to conventional diffusion (Gaussian) analysis, such as DTI. This study confines the diffusion metrics using DKI analysis of the CST in patients with iNPH. The purposes of this study were to reveal details concerning the postulated CST microstructural changes that occur in iNPH patients and to investigate the clinical utility that may assist in the diagnosis of this condition. We focused on the CST within the deep white matter of patients with iNPH and attempted to image the microstructural changes in situ using DTI and DKI.

Materials and methods

Subjects

Eleven iNPH patients (mean age 73.6 years, range 65–84 years), and six control subjects (mean age 69.8 years, range 60–75 years) were recruited and the study was conducted in accordance with the Declaration of Helsinki and approved by the appropriate institutional review board. Written informed consent was obtained from all participants or their relatives.

Diagnosis of iNPH was made by a positive spinal tap test result according to the clinical diagnostic criteria of probable iNPH [9]. Patients were excluded if they had a history of neurological disease, such as infarction or epilepsy, or if they had any underlying diseases that might affect the brain, as observed by fluid-attenuated inversion recovery scan, T1-weighted imaging, or T2-weighted imaging. These exclusion criteria were used to avoid the possibility that DTI parameters and clinical symptoms could be affected by cerebral vascular disease. Normal control subjects were required to be (a) >60 years of age, (b) have normal results on the mini-mental state examination and neurologic examination, and (c) not have any abnormal intensity observed in brain imaging by conventional magnetic resonance imaging (MRI; T1- or T2-weighted imaging).

DKI and DTI data acquisition

Both DKI and DTI datasets were acquired on a clinical 3 T-MRI scanner (Achieva Quasar Dual; Philips Medical Systems, Best, The Netherlands) with the following parameters: 3,000/80 ms TR/TE; 5-mm slice thickness; 20 sections; 256×256 mm field of view; 128×128 matrix; ~13 min and 50 s imaging time; 6 b values (0, 500, 1,000, 1,500, 2,000, and 2,500 s/mm^2) with diffusion encoding in 32 directions for every value, and a total of 192 total acquisitions. Gradient duration (δ) and the time between the two leading edges of the diffusion gradient (Δ) were 27.7 and 39.2 ms, respectively.

Tractography and tract-specific analysis of CST

Diffusion metric maps were calculated using diffusion TENSOR Visualizer software (dTV.II.FZRx; Image Computing and Analysis Laboratory, Department of Radiology, The University of Tokyo Hospital, Japan). As described in previous studies [10, 11], the DK parameters (D_{app} and K_{app}) for a single direction can be determined by acquiring datasets S at three or more b values (including b=0 and 1,000) and fitting them to the equation:

$$\ln[S(b)] = \ln[S(0)] - b \times D_{app} t + 1 \Big/ 6 \times b^2 \times D_{app}^2 \times K_{app},$$

where D_{app} is the apparent diffusion coefficient (ADC) for the given direction, and K_{app} is the apparent kurtosis coefficient and is dimensionless. The propagation of tractography was constrained by a low threshold of FA=0.18 and tractography of the CST was performed using the 2-ROI method [12]. The seed ROI was manually placed on the precentral gyrus and the target ROI was manually placed on the cerebral peduncle [13]. As an anatomic landmark for the CST, the uppermost part of the superior longitudinal fasciculus (SLF) was used instead of the lateral ventricle on the

premise that the areas where the CST and the SLF cross are not affected by the presence or absence of ventriculomegaly [12] (see Fig. 1). Voxelization was performed from the uppermost part of the SLF to the posterior limb of the internal capsule using TENSOR Visualizer. The level of the posterior limb of the internal capsule was identified at one third of the distance from the cerebral peduncle to the uppermost part of the SLF [8]. The tract-specific analysis of the CST included FA, ADC, axial eigenvalue (λ_1), radial diffusivity (RD; $\lambda_2+\lambda_3/2$), mean diffusional kurtosis (DK), axial diffusion kurtosis (ADK), and radial diffusion kurtosis (RDK).

Statistical analysis

All statistical analyses were performed using IBM SPSS statistical software (version 11.0; SPSS, Chicago, Illinois) using the Mann–Whitney *U* test. The criterion for statistical significance was $P<0.05$.

Results

The diffusion tensor and DK metrics from the periventricular segment of the CST, as measured by tract-specific analysis, are listed in Table 1. The FA values (reported as mean ± standard deviation) were significantly higher in patients with iNPH (0.661±0.058) than in the control subjects (0.581±0.027; $P<0.05$). This was also true for the ADC values (0.784±0.082 and 0.654±0.013, respectively; $P<0.005$) and the axial eigenvalues (1.492±0.121 and 1.153±0.028, respectively; $P<0.005$). The RD values were not statistically distinguishable between the iNPH patients and control individuals (0.431±0.083 and 0.405±0.022, respectively). The mean DK values (0.791±0.073 and 0.955±0.060, respectively; $P<0.005$) and the axial DK values (0.512±0.226 and 0.758±0.093, respectively; $P<0.05$) were significantly lower in iNPH patients than in control subjects. The radial DK was higher in patients than in healthy subjects; however, the values were not statistically different.

Discussion

In recent years, DKI has been used to examine brain tumors and cerebral infarction [14, 15], because it is able to depict additional information regarding tissue microstructure that is not provided by conventional diffusion analysis imaging. This study quantified the diffusion tensor metrics, including ADC, FA, axial eigenvalues, and radial eigenvalues, together with DK parameters (using DKI) of the CST in patients with iNPH. We found that ADC and FA values were significantly greater for the compressed CST of patients with iNPH than for the non-compressed CST of control subjects, consistent with previous reports [7, 8, 16]. In general, FA values are calculated from the axial and radial diffusivity of water molecules. The axial diffusivity is defined by the axial eigenvalue (λ_1), i.e., the mean magnitude of water diffusion along the axon. Radial diffusivity is defined by the radial eigenvalue (the average of λ_2 and λ_3) and represents the mean magnitude of water diffusion perpendicular to the neural axon [17]. Previous reports have shown that increased FA values in the CST indicate compaction of white matter [7, 8, 18, 19]. The increase in FA values may be caused by an increase in the diffusivity parallel to the compressed, regularly aligned fiber tracts and a simultaneous decrease in the perpendicular diffusivity, which would reflect compression of the neural axons [18].

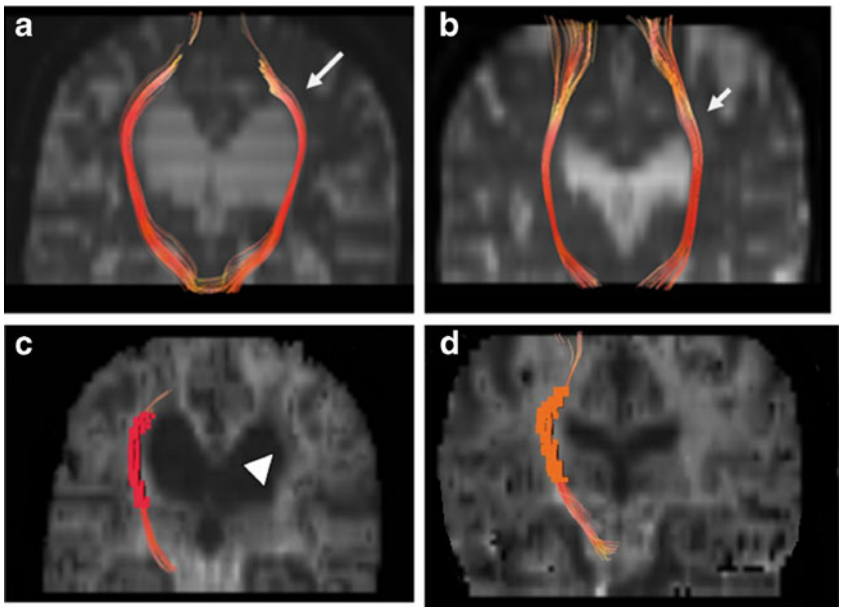

Fig. 1 Anisotropy color-coded tractography of the corticospinal tract (CST) at the level of the lateral ventricle (*arrows*) (**a**) in a patient with idiopathic normal pressure hydrocephalus (iNPH) and (**b**) in a control subject. These tractography on coronal mean kurtosis images are shown without diffusion encoding images ($b=0$ s/mm^2). Diffusional kurtosis images of (**c**) the iNPH patient and (**d**) the control subject. The diffusional kurtosis images of the iNPH patient (**c**) shows the relative low intensity (*arrow head*) of the periventricular areas compared to control subjects (**d**)

Table 1 Diffusion tensor imaging and diffusional kurtosis imaging metrics of the corticospinal tract (mean ± SD) for all subjects

	Controls	iNPH	*P* value
FA	0.581±0.027*	0.661±0.058*	0.007
ADC[10–3 mm2/s]	0.654±0.013**	0.784±0.082**	0.001
λ_1	1.153±0.028**	1.492±0.121**	0.001
RD[10–3 mm2/s]	0.405±0.022	0.431±0.083	0.763
DK	0.955±0.060**	0.791±0.073**	0.001
ADK	0.758±0.093*	0.512±0.226*	0.010
RDK	1.241±0.295	1.501±0.328	0.159

SD standard deviation, *iNPH* idiopathic normal pressure hydrocephalus, *FA* fractional anisotropy, *ADC* apparent diffusion coefficient, λ_1 axial eigenvalue, *RD* radial diffusivity, *DK* mean diffusional kurtosis, *ADK* axial diffusional kurtosis, *RDK* radial diffusional kurtosis

*P <0.05; **P <0.005

Hattori et al. hypothesized that the cerebral white matter of patients with iNPH may be compressed due to mechanical pressure caused by ventricular enlargement [8]. Such an occurrence may result in axonal stretching, which would be microscopically reflected by reduced winding and improved orientation of the neural axons. In an altered microstructure such as this, water diffusivity parallel to the axon would be enhanced, leading to an increase in the axial eigenvalue. However, in our study the radial eigenvalues were not significantly altered in patients with iNPH compared with those of control subjects. It appears that radial components for both ADC and kurtosis are increased. They are just not statistically significant, but appear to show a consistent trend. This indicates that the radial eigenvalue may be unaffected by the axonal stretching. However, the radial eigenvalue may be affected by edema in the interstitial water.

The current study demonstrated decreased DK values in the CST at the head of the lateral ventricle of iNPH patients. DK metrics including axial DK may provide further information on the structural and pathological changes in the brain in vivo [20, 21]. Jensen et al. have reported DKI can provide a model-independent kurtosis value as a means of quantifying the degree of diffusional non-Gaussianity [10]. Therefore, there was often considerable uncertainty about their validity and interpretation. Jensen et al. have reported that increased diffusional heterogeneity could explain the increase in DK value observed in acute cerebral infarction [22]. This increased value may be due to the increased microstructural complexity caused by damage or invasion of the white matter.

In this study, mechanical pressure could induce higher fiber-tract packing and an increased fiber density, lead to be microscopically uniform, which would underlie the decreased complexity and lower DK values (Fig. 2). Despite normal cellular composition of a neural axon and neural tract, the decreased DK values in the CST could be explained by the intracellular or extracellular water molecules that are less hindered in extracellular space, and unrestricted in intracellular space along the neural axon and neural tracts of these patients. These results indicate that the DK values are sensitive (i.e., same as ADC and FA

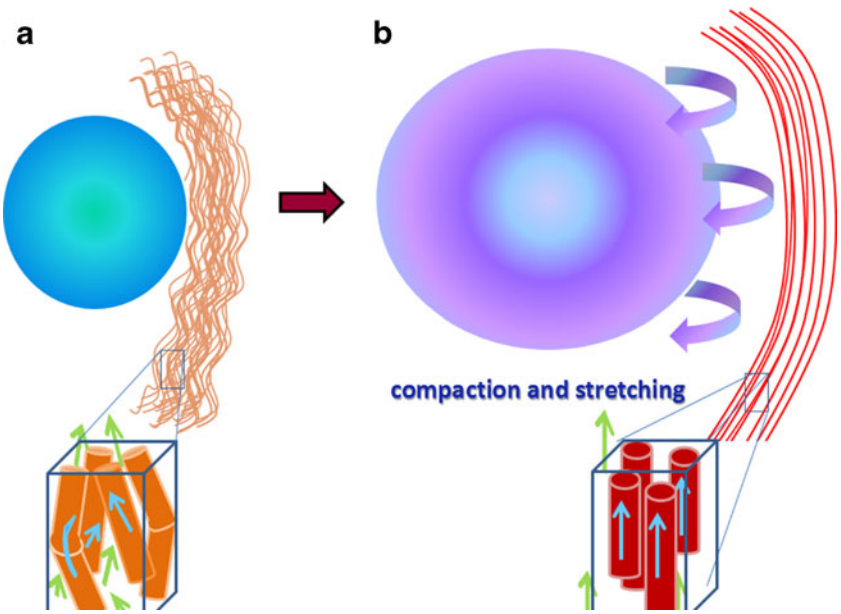

Fig. 2 Models of CST compressed by ventricular enlargement. (**a**) In normal subjects, the CST (*orange-colored* fiber tracts) could be somewhat convoluted. (**b**) In iNPH patients, the tracts (*red-colored* fiber tracts) may be compressed and stretched due to the enlargement of the ventricular system. The magnified illustrations of water diffusion in the CST in normal and idiopathic normal hydrocephalus; the decreased DK values in the CST of the iNPH could be explained by the intracellular (*blue*) or extracellular (*green*) water molecules that are less hindered in extracellular space, and unrestricted in intracellular space along the neural axon and neural tracts

values in iNPH) and these values may have different additional microstructural information about intra- or extracellular water molecular movement [14, 15, 23–28].

Our study has some limitations, the first being the limited number of iNPH patients enrolled. Secondly, our study was lack of clinical correlation. Correlation between diffusion metrics and treatment outcome is important for the establishment of DKI as a clinical biomarker, in particular. Future studies that include more iNPH patients with ventricular enlargement are therefore necessary to validate the findings of our study. Further investigation is also required to correlate DK values with their corresponding clinical characteristics in order to monitor changes during follow-up examinations and to predict patient prognosis.

In conclusion, this study found that the decreased DK values at the level of the lateral ventricle of the CST were significantly greater in patients with iNPH than in control subjects. In addition, the increased ADC and axial eigenvalue were also significantly greater. These results indicate an altered microstructure and retention of intracellular and extracellular water molecules in the CST of these patients, presumably resulting from the mechanical pressure caused by ventricular enlargement. This may occur with or without a decrease in the abundance of crossing fibers. DKI imaging of the CST may therefore provide a noninvasive, accurate means for diagnosing iNPH.

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Conflict of interest We declare that we have no conflict of interest.

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