Comparison of Microfiber Alteration of Corticospinal Tract in Normal Pressure Hydrocephalus Patients and Normal Controlled Subjects by Diffusion Tensor Imaging

Chanon Ngamsombat MD*, Zhe Zhang PhD**,
Hua Guo PhD**, Khittinee Lerdthusnee MD*,
Theerapol Witthiwej MD***, Weerasak Muangpaisan MD****, Jitsupa Wongsripuemtet MD*,
Yudthaphon Vichianin PhD*****, Panida Charnchaowanish BSc*, Orasa Chawalparit MD*

** Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*
*** Center for Biomedical Imaging Research, Department of Biomedical Engineering, School of Medicine, Tsinghua University, Beijing, China*
**** Division of Neurosurgery, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*
***** Department of Preventive and Social Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*
****** Department of Radiological Technology, Faculty of Medical Technology, Mahidol University, Bangkok, Thailand*

Background: *Idiopathic normal pressure hydrocephalus (iNPH) is one of the treatable causes of dementia in elderly by shunt placement surgery. Diffusion tensor imaging (DTI) can demonstrate the alteration of white matter microfiber. The corticospinal tract (CST) is white matter fiber responsible in part of motor function and gait.*

Objective: *This study was to compare microfiber alteration of the CST between iNPH patients and normal controlled subjects.*

Material and Method: *Fifteen clinically diagnosed definite iNPH patients and 15 normal controlled subjects underwent MRI study with DTI. All iNPH patients had gait disturbance and clinical improvement after shunt placement surgery. Probabilistic tractography of the CST were performed and comparison of DTI parameters included fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) in iNPH and normal controlled groups.*

Results: *There were statistically significant increase of MD ($p<0.001$), AD ($p<0.001$) and RD ($p<0.001$) in iNPH patients compared with normal controlled subjects, whereas FA of iNPH patients was slightly decreased but not statistically significant different when compared with the normal controlled group ($p = 0.75$).*

Conclusion: *DTI parameters, especially MD, AD and RD can be used to evaluate alteration of white matter microfiber of the CST, which was responsible in part of alteration of motor function and gait disturbance in iNPH patients. We hope that our study will lead to further investigation about other role of DTI in iNPH patients.*

Keywords: *Normal pressure hydrocephalus, Diffusion tensor imaging, Corticospinal tract*

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Nowadays dementia has been known as one of the most common geriatric conditions caused by many etiologies. In general, dementia has been categorized to treatable and non-treatable dementia and this is clinically significant. For treatable dementia, normal pressure hydrocephalus (NPH) is one of the surgically correctable causes[1] and can be improved by insertion of ventriculo-peritoneal shunt. NPH consists of the clinical triad, including dementia, gait disturbance and urinary incontinence with radiographic communicating hydrocephalus. NPH was also categorized into primary or idiopathic NPH (iNPH) and secondary NPH, which the latter has certain intracranial pathologies such as previous brain trauma, subarachnoid hemorrhage or meningitis.

There is still overlap in diagnosis of NPH, especially iNPH with degenerative change in the elderly or other neurodegenerative diseases. The correlation with other clinical history is also important. The symptoms of NPH are compromised by dilatation of the ventricular system. It also causes a pressure effect

Correspondence to:
Chawalparit O, Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.
Phone: +66-2-4197086, Fax: +66-2-4127785
E-mail: oak_art@yahoo.com, orasa.cha@gmail.com

and compromises adjacent white matter fiber functions, especially in the corticospinal tract (CST) corresponding to motor function or the posterior cingulate gyrus corresponding to cognitive function.

Magnetic resonance imaging (MRI) also plays a major role for the diagnosis. It is important for early diagnosis of iNPH since most patients are proved to have good response to shunt placement and leading to better quality of life, especially in the early stage(2). Many studies have been performed worldwide throughout the recent decade to improve the sensitivity of imaging techniques for iNPH diagnosis. Advanced MRI techniques have been applied and designed for early diagnosis of iNPH to be powerful predictor for best treatment in these patients.

Diffusion tensor imaging (DTI), new advanced imaging techniques, have been widely used for evaluating white matter tract lesions(3) and also useful in iNPH in regards to presurgical evaluation and prediction of postoperative outcome(4). By DTI technique, directional movement of water molecules in these particular white matter tracts can be measured with several parameters, including fractional anisotropy (FA), mean diffusivity (MD), apparent diffusion coefficient (ADC), mean axial and mean radial diffusivity (AD and RD), in order to determine microstructural changes(5). The CST is one of the white matter fiber tracts corresponding to motor function and gait, and it is suspected to have microstructural alteration in patients with iNPH(6). To current knowledge, in Thailand, there has still been a lack of descriptive or comparative study about microstructural alterations of white matter tract in iNPH patients.

According to collaboration between Department of Radiology, Division of Neurology, Department of Medicine, Division of Neurosurgery, Department of Surgery and Department of Psychiatry, Faculty of Medicine Siriraj Hospital, Mahidol University, the predictor of pretreatment imaging study, clinical diagnosis and clinical improvement to shunt placement have been studied since 2011(7-10). Therefore, to select the best surgical candidate, the objective of this study was to compare microfiber alteration of the CST in iNPH patients and normal controlled subjects in Thai population. This might be used for monitoring and evaluation of interval changes of the disease after surgical treatment.

Material and Method

Study designs and subjects

The study was approved by the Siriraj Institutional Review Board. A retrospective review was done during 2014 to 2015 and 15 patients with clinically diagnosed as definite iNPH (9 males and 6 females, mean age 77.1 years old) and 15 normal controlled subjects (8 males and 7 females, mean age 56.9 years old) were included in this study. Clinical information were reviewed and collected for demographic data (sex and age), duration of symptoms, underlying disease, Thai Mental State Examination score (TMSE score), Japanese NPH grading system (JGS)(11) especially gait disturbance in before and after shunt placement.

All iNPH patients were diagnosed as definite iNPH from clinical presentations and diagnostic criteria of iNPH in Guidelines for Management of Idiopathic Normal Pressure Hydrocephalus: Second Edition(12). Normal controlled subjects were selected from Siriraj Thai Language Paradigm for Functional MRI: A Pilot Study in Normal Volunteers project(13) and other normal controlled subject were recruited from patients who underwent MRI study due to non-specific symptoms, such as headache or vertigo with exclusion of clinical dementia and imaging studies showing normal result or no significant abnormality, such as infarction, hemorrhage or abnormal mass lesion. All of normal controlled subjects have normal neurological examination and no gait disturbance. All of the iNPH patients and normal controlled subjects have no significant white matter hyperintensity on MRI according to the modified criteria of Fazekas et al(14).

Characteristics of both groups were reviewed in demographic data (sex and age) and underlying disease. While in the iNPH group, duration of symptoms, TMSE score and JGS, especially gait disturbance before and after shunt placement, were also reviewed.

MRI techniques and DTI processing

All subjects underwent MRI study (3.0 tesla MR system, Ingenia, Philips Medical System, Best, The Netherlands) with 32-channel head coils. DTI study was obtained by a single shot, diffusion weighted spin echo EPI sequence; 32 diffusion encoding directions; diffusion weighting factor b = 800 s/mm^2 in addition to a single reference image (b = 0); acquisition matrix 112x112; FOV 22.4 cm; voxel size = 2 mm (RL) x 2 mm (AP) with 60 contiguous slices with slice thickness of 2 mm; Acquisition time was 12: 14 min. DICOM data of each iNPH patient and normal controlled subject were collected for analysis. Post processing DTI data were performed by using FSL (FMRIB software Library version 5.0.8)(15). The diffusional raw data were processed, including brain extraction and correction for eddy current distortions. Then dtifit-for local fitting of diffusion tensors and bedpostx- for local modeling of diffusion parameters were performed, respectively and fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) maps were obtained.

For probabilistic tractography of the CST, region of interest (ROI) were employed to confine fiber tracts in each subject in standard space, comprising of a seed mask, a waypoint mask, a target mask and an exclusion mask. For a seed mask, bilateral primary motor cortex (M1)[16] were defined by voxels covering about caudal half of the precentral gyrus (motor cortex) and along the anterior wall of the central sulcus, according to the Harvard-Oxford Atlas in the standard space. For a waypoint mask, the lower pons ipsilateral to each M1 regions was delineated in each subject in the standard space. For an exclusion mask, the corpus callosum and cerebellum were used, in order to remove interhemispheric and cerebellar trajectories. As a setting of 5,000 streamlines repetitively calculating from each voxel of the seeding mask was via the waypoint masks to the target masks (seed mask to waypoint mask to target mask). By the connectivity distribution, each voxel had a streamline count passing through and each image were transformed into the standard space via forward deformation and probtrackx were used for probabilistic tractography and connectivity-based segmentation of corticospinal tract. Comparison of DTI parameters, including FA, MD, AD and RD between iNPH patients and normal controlled subjects were performed.

Statistical analysis

The result data were analyzed by using the Statistical Package for Social Sciences, version 21 (SPSS Inc, Chicago, Illinois). Comparison data among these groups were performed by using one-way ANOVA with a post hoc Tukey Honestly Significant Difference test or Games-Howell for continuous variables, the Kruskal-Wallis test with post hoc Mann-Whitney U tests for non-continuous variables, and the χ^2 test for categorical data. The criterion of statistical significance was $p<0.05$.

Results

The duration of symptoms, TMSE score and JGS, especially gait disturbance before and after shunt placement of iNPH patients were shown in Table 1. All of iNPH patients had improvement of gait disturbance after shunt placement surgery. All of iNPH patients had diffuse dilatation of the ventricular system and Evan's index >0.3.

In comparison of DTI parameters of the CST, there were statistically significant difference of MD ($p<0.001$), AD ($p<0.001$) and RD ($p<0.001$) between iNPH patients and normal controlled subjects. Whereas FA of iNPH patients was slightly decreased but not statistically significant different from FA of the controlled group ($p = 0.75$) (Table 2, Fig. 1, 2).

Discussion

Various studies about the role of advanced MRI in NPH have been published worldwide. Bradley et al studied iNPH patients with MRI CSF flow study[17]. His study was one of the early studies about imaging guidance techniques for diagnosis of iNPH and to understanding the pathophysiology of the disease. They suggested that CSF stroke volume obtained by CSF flow study was helpful for selecting patient for shunt placement surgery. Witthiwej et al studied intracranial hydrodynamics and ventriculo-peritoneal shunt responsiveness and described MRI parameters as a predictor for shunt responsive cases in patient with normal pressure hydrocephalus by means of MRI CSF flow[7]. Regarding their study, the mean velocity and peak velocity were significant values for shunt responsiveness prediction. Also, Witthiwej et al reported a study of MRI morphologic features and CSF flow study to predict shunt responsiveness in patients with NPH and revealed that severity of white matter change and CSF flow analysis could predict shunt-responsive cases[9]. Ngamsombat et al compared between shunt responsive and shunt non-responsive groups of NPH by using DTI and found that the responsive group had a trend of higher FA and lower ADC than the non-responsive group[10].

In our study, the DTI parameters, especially MD, AD and RD could demonstrate the alteration of the CST. Based on hypothesis that DTI parameters can be used to display microstructural alteration caused by pressure effect to the adjacent white matter from dilated ventricular system as well as interstitial edema from transependymal effusion.

These changes probably affect axonal and myelin integrity of the CST as shown in our study. The axonal stretching caused by the dilated ventricle leads to increased tightness of the CST shown as increased AD parameter. An increased RD parameter in the iNPH group can be explained by interstitial edema, some degree of myelination integrity loss and minor or reversible ischemic change of the whiter matter fiber.

Table 1. Demographic and clinical characteristics of iNPH patients

Patient No.	Sex	Age (yr)	TMSE score	JGS score	Gait disturbance score before shunting	Gait disturbance score after shunting	Duration of symptoms (mo)	Underlying diseases
1	M	85	-	5	4	3	12	DM, HT, CKD, cholesteatoma, glaucoma, gout, BPH
2	M	71	13/30	7	3	3 with speed improvement	12	Old CVA, CAD, DM
3	F	78	25/30	8	4	3	24	DM, HT, DLP
4	M	70	15/30	8	3	2	4	Parkinson disease
5	M	76	19/30	9	2	1	12	-
6	M	73	24/30	9	3	1	24	Old CVA
7	F	70	24/30	11	3	3 with stability improvement	48	BPD, subclinical hypothyroidism, neurogenic bladder
8	M	75	27/30	9	3	2	60	DM, HT, DLP, DCM, BPH, old CVA
9	M	84	13/30	7	3	2	12	Prostate cancer, MDD, CAD, old CVA, CHF
10	F	88	10/30	9	3	1	24	-
11	F	78	14/30	12	4	3	12	HT, primary hyperparathyroidism
12	M	86	27/30	8	4	3	12	-
13	M	77	25/30	8	3	3 with speed improvement	12	-
14	F	64	10/30	10	3	3 with stability improvement	12	DM, HT, DLP, Old CVA
15	F	81	6/30	11	3	2	12	DM, HT, DLP

BPD = bipolar disorder; BPH = benign prostate hyperplasia; CAD = coronary artery disease; CHF = congestive heart failure; CKD = chronic kidney disease; CVA = cerebrovascular accident; DLP = dyslipidemia; DCM = dilated cardiomyopathy; DM = diabetes mellitus; HT = hypertension; MDD = major depressive disorder

Table 2. Comparison of DTI parameters of the corticospinal tract (display in mean ± standard deviation, minimum and maximum values) between iNPH patients and normal controlled subjects

DTI parameters (mm/s^2)	iNPH patients	Normal controlled subjects	*p*-value
FA	0.398±0.049 (0.332 to 0.506)	0.431±0.049 (0.345 to 0.495)	0.075
MD ($x10^{-3}$)	1.049±0.124 (0.854 to 1.268)	0.825±0.066 (0.731 to 0.950)	<0.001*
AD ($x10^{-3}$)	1.495±0.124 (1.304 to 1.602)	1.219±0.052 (1.147 to 1.331)	<0.001*
RD ($x10^{-3}$)	0.826±0.137 (0.734 to 1.024)	0.626±0.077 (0.514 to 0.758)	<0.001*

FA = fractional anisotropy; MD = mean diffusivity; AD = axial diffusivity; RD = radial diffusivity
* Indicates statistical significance

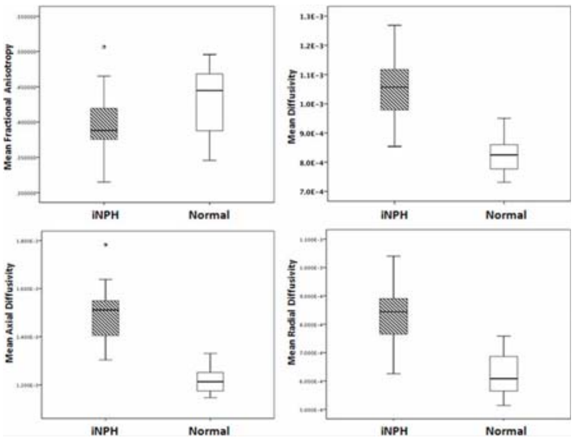

Fig. 1 Comparison of DTI parameters between iNPH patients and normal controlled subjects by independent-sample Kruskal-Wallis test.

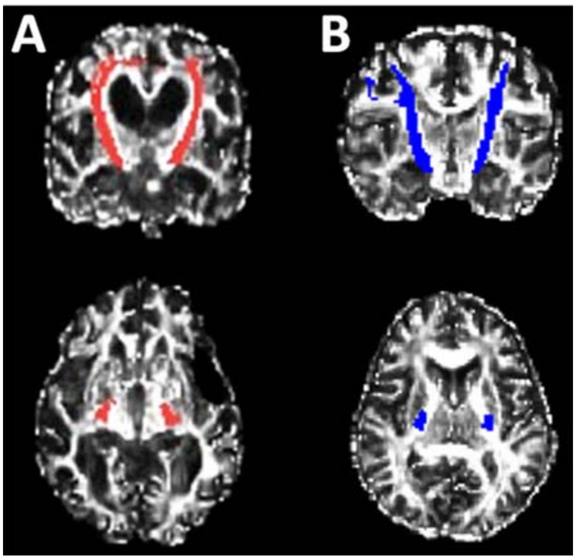

Fig. 2 Probabilistic tractography of the bilateral corticospinal tracts in coronal and axial views show bowing or stretching of the bilateral corticospinal tracts laterally due to pressure effect by diffuse ventricular dilatation in iNPH patient (A) compared with normal controlled subject (B).

These mechanisms might describe subgroup of patients with partially improvement of gait disturbance in iNPH. Moreover, this reversible change is helpful for identifying patients who might have benefit from shunt placement surgery.

In our study, FA has no statistically significant difference between iNPH patients and normal controlled subjects as also shown in previous study. Marumoto et al reported significant lower FA of the CST compared with the Parkinson's disease and healthy control groups [18]. Whereas most studies about DTI parameters in iNPH showed increased FA in iNPH group compared with normal controlled group. Assaf et al showed that the FA was increased in the white matter areas lateral to the ventricles in acute hydrocephalus. The increased volume of the cerebrospinal fluid in hydrocephalus frequently leads to pressure on most adjacent white fiber pathway[19]. Osuka et al used DTI in patients with chronic idiopathic hydrocephalus and showed that increased FA in the CST was a specific finding in definite iNPH, but not in ventriculomegaly associated with brain atrophy[20]. Hattori et al also showed increased FA values in the CST of patients with iNPH[21].

In our study, factors influencing FA measurement, such as chronic minor white matter ischemia might not demonstrate signal abnormality in conventional MRI study. The difference in mean age between iNPH and normal controlled subject groups and associated degenerative white matter change and other co-morbidity such as hypertension, diabetes mellitus or other small vessel diseases could be the confounders of the study and were the limitation of precise comparison between both groups.

The limitation of this study included retrospective nature and different age group. The iNPH group had higher mean age than normal controlled subject group. Therefore, degenerative change and associated chronic disease in the elderly might be influencing confounders.

Conclusion

The multiple DTI parameters (MD, RD and AD) showed statistically significant differences between iNPH patients and normal controlled subjects and could be used to evaluate alteration of white matter microfiber of the CST, which is responsible for alteration of motor function and gait disturbance in iNPH patients. We hope that our study will lead to further investigation about other role of DTI in iNPH patients.

What is already known on this topic?

iNPH is a treatable chronic degenerative condition commonly found in the elderly population. The diagnosis principally bases on clinical examination and brain imaging studies. Of the various neuroimaging studies, DTI is increasingly utilized in diagnosis of iNPH.

What this study adds?

The DTI parameters can be used as an adjunctive tool for evaluation of iNPH. Difference in these parameters was found between iNPH patients and normal subjects. Bowing or stretching of the CST seen in the DTI can explain the occurrence of impaired motor function and gait disorder in patients with iNPH.

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Potential conflicts of interest

None.

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การศึกษาเปรียบเทียบการเปลี่ยนแปลงของใยประสาทขนาดเล็กในแนวประสาทควบคุมการเคลื่อนไหวในผู้ป่วยโพรงสมองคั่งน้ำชนิดความดันปกติและกลุ่มประชากรควบคุมโดยใช้การตรวจ diffusion tensor imaging

ชนน งามสมบัติ, Zhe Zhang, Hua Guo, กฤตินี เลิศทัศนีย์, ธีรพล วิทธิเวช, วีรศักดิ์ เมืองไพศาล, จิตสุภา วงศ์ศรีภูมิเทศ, ยุทธพล วิเชียรอินทร์, พนิดา ชาญเชาว์วานิช, อรสา ชวาลภาฤทธิ์

ภูมิหลัง: *ภาวะโพรงสมองคั่งน้ำชนิดความดันปกติ ซึ่งไม่ทราบสาเหตุเป็นสาเหตุหนึ่งของภาวะสมองเสื่อมที่สามารถรักษาได้โดยการผ่าตัดใส่อุปกรณ์ระบายน้ำในสมองและไขสันหลังการตรวจ diffusion tensor imaing สามารถเห็นการเปลี่ยนแปลงของใยประสาทขนาดเล็กของแนวประสาทในสมองพบว่าแนวประสาทควบคุมการเคลื่อนไหวเป็นส่วนของแนวประสาทในสมองที่เกี่ยวข้องกับการสั่งการและการเดิน*

วัตถุประสงค์: *เพื่อเปรียบเทียบการเปลี่ยนแปลงของใยประสาทขนาดเล็กในแนวประสาทควบคุมการเคลื่อนไหวระหว่างกลุ่มผู้ป่วยโพรงสมองคั่งน้ำชนิดความดันปกติซึ่งไม่ทราบสาเหตุและกลุ่มประชากรควบคุม*

วัสดุและวิธีการ: *ผู้ป่วย 15 รายได้รับการวินิจฉัยว่าเป็นโรคโพรงสมองคั่งน้ำชนิดความดันปกติซึ่งไม่ทราบสาเหตุและ 15 รายอยู่ในกลุ่มประชากรควบคุม ผู้ป่วยทั้งหมดได้รับการตรวจภาพแม่เหล็กไฟฟ้าและ diffusion tensor imaging ของสมอง ในกลุ่มผู้ป่วยที่เป็นโรคผู้ป่วยทุกรายมีการเดินผิดปกติก่อนผ่าตัด และมีอาการดีขึ้นหลังผ่าตัดใส่อุปกรณ์ระบายน้ำในสมองและไขสันหลังได้ทำการตรวจ diffusion fiber tractography ของแนวประสาทควบคุมการเคลื่อนไหว และเปรียบเทียบค่าต่างๆ ของ diffusion tensor imaging ได้แก่ fractional anisotropy, mean diffusivity, axial diffusivity และ radial diffusivity ทั้งในกลุ่มผู้ป่วยและกลุ่มประชากรควบคุม*

ผลการศึกษา: *พบว่ากลุ่มผู้ป่วยการเพิ่มขึ้นของค่า mean diffusivity ($p<0.001$), axial diffusivity ($p<0.001$) และ radial diffusivity ($p<0.001$) อย่างมีนัยสำคัญทางสถิติเมื่อเปรียบเทียบกับกลุ่มประชากรควบคุม ในขณะที่กลุ่มผู้ป่วยมีการเพิ่มของค่า fractional anisotropy เพียงเล็กน้อยซึ่งไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ เมื่อเปรียบเทียบกับกลุ่มประชากรควบคุม ($p = 0.75$)*

สรุป: *ค่าของการตรวจ diffusion tensor imaging โดยเฉพาะค่า mean diffusivity, axial diffusivity และ radial diffusivity สามารถใช้ประเมินการเปลี่ยนแปลงของใยประสาทขนาดเล็กในแนวประสาทควบคุมการเคลื่อนไหว ซึ่งแนวประสาทนี้มีส่วนสำคัญในการเปลี่ยนแปลงของการสั่งการและการเดินที่ผิดปกติในผู้ป่วยโพรงสมองคั่งน้ำชนิดความดันปกติซึ่งไม่ทราบสาเหตุ คณะผู้นิพนธ์หวังว่างานวิจัยนี้จะนำไปสู่การศึกษาเพิ่มเติมเกี่ยวกับบทบาทของ diffusion tensor imaging ในผู้ป่วยโพรงสมองคั่งน้ำชนิดความดันปกติซึ่งไม่ทราบสาเหตุ*