Comparison of Microfiber Alteration of Fornix in Idiopathic Normal Pressure Hydrocephalus Patients, Alzheimer's Disease Patients and Healthy Volunteers *via* Diffusion Tensor Imaging

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Abstract

Purpose: The clinical and imaging findings of idiopathic normal pressure hydrocephalus (iNPH) and Alzheimer's disease (AD) patients have some overlap and are often challenging to diagnose. The fornix is an important structure in the memory function, and damage to the fornix can result in memory impairment. Our study aimed to explore any differences in the microstructural changes to the fornices of iNPH and AD patients relative to those of normal control subjects, as demonstrated by using diffusion tensor imaging (DTI).

Materials and methods: Ten normal control subjects, 10 iNPH patients and 10 AD patients underwent MRI scans (3-Tesla), and the DTI data were obtained. The DTI parameters and the diffusion fiber tractography were derived using DSI studio software. The differences in the fractional anisotropy (FA), apparent diffusion coefficient (ADC), axial diffusivity, and radial diffusivity data of the three groups were compared. A receiver operating characteristic (ROC) curve analysis was also evaluated.

Results: There was a statistically-significant lower mean FA for the iNPH and AD patients than the normal control subjects. The mean ADC of the iNPH patients was statistically significantly higher than that of both the normal control subjects and the AD patients. The mean ADC is probably the most helpful parameter evident from our results, given its high sensitivity and high negative predictive value for discriminating between iNPH and AD patients.

Conclusion: Our study revealed different microstructural changes in the fornices of iNPH and AD patients using the DTI technique. The results are probably due to differences in the pathogenesis of the diseases. Furthermore, our study demonstrated the possibility of using the DTI parameter as a supportive tool to discriminate between iNPH and AD patients with high sensitivity and a high negative predictive value.

Keywords: Fornix; Diffusion tensor imaging; Idiopathic normal pressure hydrocephalus; Alzheimer's disease

Abbreviations: DTI: Diffusion Tensor Imaging; FA: Fractional Anisotropy, ADC: Apparent Diffusion Coefficient; ROI: Region of Interest; iNPH: Idiopathic Normal Pressure Hydrocephalus; AD: Alzheimer's Disease

Introduction

The fornix is an arch-shaped, white-matter tract carrying the output fibers of the hippocampus to the mamillary bodies and septal nuclei. It is composed of the crura, the commissure, the body, and the columns [1,2]. The fornix is recognized as a part of the Papez circuit [3], and it plays a vital role in the memory function [4]. Damage to the fornix can result in memory impairment.

DTI is an advanced MRI technique that can be used to investigate early microstructural changes in the brain. Through this technique, the degree of anisotropy of the directional movement of water molecules in particular white matter fibers can be derived and measured with fractional anisotropy (FA), apparent diffusion coefficient (ADC) and fiber tractography. DTI is widely used to evaluate the integrity of various white matter tracts following microstructural changes.

The most common cause of neurodegenerative dementia is Alzheimer's disease. The pathophysiology begins at the entorhinal cortex with neurofibrillary tangle deposits and neuronal loss. The fornix alteration occurring during Alzheimer's disease has been histologically proven to be due to neurodegeneration, and the alteration has been recently demonstrated with FA and mean diffusivity (MD) changes using the DTI technique [5-9]. Furthermore, many studies have demonstrated a correlation between FA changes and cognitive function which can be used to predict clinical outcomes.

iNPH is one of the few, treatable causes of dementia, and it was first described by Hakim and Adams in 1965 [10]. Patients present with the classic signs and symptoms of gait disturbance, urinary incontinence, and dementia, and the disease is associated with an imaging finding of ventricular enlargement without elevated cerebrospinal fluid (CSF) pressure. Both the clinical presentations and the radiographic findings of iNPH and Alzheimer's disease overlap, making diagnosis often challenging for neurologists and neurosurgeons. Many previous studies have demonstrated an FA change in the fornix of patients with Alzheimer's disease, but few studies have investigated the white matter integrity of iNPH patients [11,12], particularly in the fornix.

Based on the differences in the pathophysiology of these two diseases, we hypothesized that the pattern of white matter tract change might be different in terms of the DTI parameters. We were interested in the fornix fiber because the anatomy of the fornix is very close to the ventricle, which might be one of the most affected tracts and might explain the clinical signs of cognitive impairment evident among iNPH patients.

To date, no study has compared alterations in the fiber tracts of normal, healthy individuals with those of Thai iNPH and Alzheimer's disease patients. The objective of this study was to explore any microfiber alteration of the fornix among those groups by using diffusion tensor imaging. Furthermore, the study aimed to investigate which DTI parameter(s) could be used to characterize those two diseases.

Materials and Methods

Subject selection

The study was approved by the Siriraj Institutional Review Board. Ten control subjects (6 males and 4 females; mean age 59.0 years; age range 50-72 years) were enrolled. Five of those subjects were part of the study "Thai Language Paradigm for Functional MRI: A Pilot Study in Normal Volunteers" [13], while the other five were undergoing an MRI study due to having non-specific symptoms (like headache or vertigo), with no abnormal neurological examination and no gross MRI abnormality (such as infarction, hemorrhage or tumor mass lesions). The ten iNPH patients (6 males and 4 females; mean age 74.4 years; age range 62-88 years) were diagnosed using the diagnostic criteria for idiopathic normal pressure hydrocephalus [14]. The third group of ten patients were diagnosed with probable Alzheimer's disease dementia, based on the NINCDS-ADRDA criteria 2011 [15] (5 males and 5 females; mean age 77.1 years; age range 70-82 years). All of the normal controlled subjects, iNPH and AD patients and have no significant white matter hyperintensity on MRI according to the modified criteria of Fazekas et al. [16]. Exclusion criteria is Fazekas score >1 to exclude small vessel disease.

MR imaging data acquisition

The MRI scans were performed on two machines. The first was a 3.0 Tesla MR system (Achieva, Philips, the Netherlands), with an 8-channel head coil. The DTI study was obtained with a single shot, diffusion-weighted spin echo EPI sequence; 32 diffusion encoding directions; diffusion weighting factor b=800 s/mm² in addition to a single reference image (b=0); acquisition matrix 112 × 112; FOV=22.4 cm; voxel size=2 mm (RL) × 2 mm (AP), with 60 contiguous slices with a slice thickness of 2.3 mm; TR=10,371 ms; TE=54 ms; flip; and angle=90°. The acquisition time was 12:39 min.

The second machine was a 3.0 Tesla MR system (Ingenia, Philips Medical System, Best, the Netherlands), with a 16-channel head coil. The DTI study was obtained with a single shot, diffusion-weighted spin echo EPI sequence; 32 diffusion encoding directions; diffusion weighting factor b=800 s/mm² in addition to a single reference image (b=0); acquisition matrix 112 × 112; FOV=22.4 cm; voxel size=2 mm (RL) × 2 mm (AP), with 60 contiguous slices with a slice thickness of 2.0 mm; TR=9,978 ms; TE=104 ms; flip; and angle=90°. The acquisition time was 12:14 min.

3D-T1 weighted image and fluid-attenuated inversion recovery images were obtained for all patients. In the case of the Alzheimer's patient group, a coronal oblique T1 weighted image at right angles to the longitudinal axis of the hippocampus was also obtained.

Data analysis

The DTI data were processed and analyzed to perform a diffusion tractography of the fornix with DSI Studio software [17] The method to draw the ROI was based on a basic knowledge of normal anatomy and previous literature [18-21]. In this study, seeding and target ROIs based on paths between two ROI methods were chosen. The ROIs were manually outlined on color images of the major diffusion tensor eigenvector (red=left–right, green=anterior–posterior, and blue=superior–inferior). The first ROI was placed at the crus of the fornix in the coronal plane, which is the most obvious, discrete, green-colored fiber (**Figure 1A**). The second ROI was placed in the most-anterior coronal view where the body part is visible (a green to blue color, as it is curved);

see **Figure 1B**. A deterministic tractography was done on the right and the left fornix, separately (**Figure 2**), with a threshold FA value of at least 0.15 and a threshold angle of 60 degrees [5,7,18,22]. The mean FA, ADC, and the axial and radial diffusivities were measured on the left and right fornix, separately. The average of the left- and right-side values was calculated for each parameter. Two investigators performed the tractography using the same method; one of the researchers was a neuroradiologist, and the other was a fellow in neuroradiology. After the tractography was done, the derived fornix tract was compared with the 3D-T1 weighted image to confirm the fiber pathway.

Statistical analysis

The resulting data were analyzed by using the Statistical Package for Social Sciences, Version 21 (SPSS Inc, Chicago, Illinois). A comparison of the data of those groups was performed by using one-way ANOVA with a post-hoc Tukey's Honestly Significant Difference test or Games-Howell for the continuous variables; the Kruskal-Wallis test with post-hoc Mann-Whitney U tests for the non-continuous variables; and Pearson's chi-squared test for the categorical data. The criterion of statistical significance was $p < 0.05$.

The area under the curve (AUC) was calculated from the receiver operating characteristic (ROC) by identifying the optimal cutoff value to distinguish iNPH from Alzheimer's disease. The size of the area under the ROC curve represented the strength of the cutoff value between the FA, ADC, the mean axial and radial diffusivities, and the diagnostic performance. The PPV (positive predictive value) and NPV (negative predictive value) were also computed.

The interobserver reliability was examined by using the intraclass correlation coefficient (ICC). A kappa (κ) score of less than or equal to 0.4 indicated poor reliability, 0.41-0.59 fair reliability, 0.60-0.74 good reliability, and 0.75-1.00 excellent reliability.

Results

The patients' demographic data are at **Table 1**. The mean age of the control group was statistically significantly lower than those of the iNPH and AD groups ($p < 0.01$). However, there was no significant difference in the mean ages of the iNPH and AD groups (p=0.67). There was also no significant difference in the genders of the three groups.

The vascular risk factors were recorded. The incidence of hypertension in the control group was statistically significantly lower than in the iNPH and AD groups ($p < 0.01$), but there was no

significant difference between the iNPH and AD groups (p=0.63). The incidence of diabetes mellitus was statistically significantly lower in the control group than in the iNPH group (p=0.03), but there was a significant difference between the AD group and both the control group (p=0.07) and the iNPH group (p=0.66).

There was a statistically significant lower incidence of dyslipidemia in the control group than in the Alzheimer's disease group (p=0.02). In contrast, there was no significant difference between the control and the iNPH groups (p=0.12), and between the iNPH and the AD groups (p=0.36).

The Evan's index of all of the control and Alzheimer's disease subjects did not exceed 0.3. Almost all iNPH patients had an Evan's index more than 0.3. The only iNPH patient who had a lower Evan's index (0.29) presented with gait disturbance and urinary incontinence; this patient had shown clinical improvement after a tap test and had been diagnosed as probable iNPH. Seven patients had improved clinically after a ventriculostomy shunt and had been diagnosed as definite iNPH. Another two patients were diagnosed with possible iNPH.

The derived DTI parameters from the tract-specific analysis of the tractography of the fornix are demonstrated at **Table 2** and **Figure 3**. The mean FA of the control group was significantly higher than those of both the iNPH group ($p < 0.001$) and the Alzheimer's group (p=0.01). Although the mean FA of the iNPH group was lower than that of the Alzheimer's group, there was no statistical significance (p=0.266).

The mean ADC of the control group was significantly lower than that of the iNPH group ($p < 0.001$). The mean ADC of the iNPH group was significantly higher than that of the Alzheimer's group (p=0.047). There was no significant difference in the mean ADC of the control and AD groups (p=0.535).

There were statistically significant higher mean axial and radial diffusivities for the iNPH group than the control group (p=0.003 and $p < 0.001$, respectively). However, there were no significant differences in the mean axial and radial diffusivities of the control and the AD groups, or of the iNPH and the AD groups ($p > 0.05$).

The interobserver reliability was excellent for all of the DTI parameters, with a kappa score of 0.958 for the mean FA, 0.898 for the mean ADC, 0.877 for the mean axial diffusivity, and 0.909 for the mean radial diffusivity.

Discussion

The fornix is a part of the Papez circuit and plays an important

Table 1 Demographic and clinical data of control subjects and of iNPH and Alzheimer's disease patients.

Characteristics	Control (n=10)	iNPH (n=10)	Alzheimer's disease (n=10)
Age (years ± SD)	59 ± 7.4	74.4 ± 8.5	77.1 ± 4.6
Gender male: female	6:4	6:4	5:5
Evans' index	0.25 ± 0.02	0.33 ± 0.04	0.28 ± 0.02
Vascular risk factors			
Hypertension (number of patients)	1	7	8
Diabetes mellitus (number of patients)	0	4	3
Dyslipidemia (number of patients)	3	6	8

Table 2 Tract-specific analysis of tractography of the fornix.

Parameter	Control (n=10)	iNPH (n=10)	AD (n=10)	p-value*		
				Control *vs.* iNPH	Control *vs.* Alzheimer's disease	iNPH *vs.* Alzheimer's disease
Mean FA	0.3746 ± 0.01943	0.2322 ± 0.03334	0.2849 ± 0.03968	<0.001†	0.010†	0.266
Mean ADC	1.8896 ± 0.23707	2.7067 ± 0.33466	2.1917 ± 0.44779	0.001†	0.535	0.047†
Mean axial diffusivity	2.5459 ± 0.30622	3.3047 ± 0.37428	2.7773 ± 0.50424	0.003†	1.000	0.058
Mean radial diffusivity	1.5615 ± 0.20473	2.4077 ± 0.31974	1.8989 ± 0.42186	<0.001†	0.364	0.051

Data are shown as mean ± SD
Mean ADC, axial and radial diffusivity are shown in 10^{-3} mm²/s
*p-value from the Kruskal-Wallis test; †Statistical difference, $p<0.05$

Table 3 Threshold values and diagnostic discrimination between iNPH and AD groups.

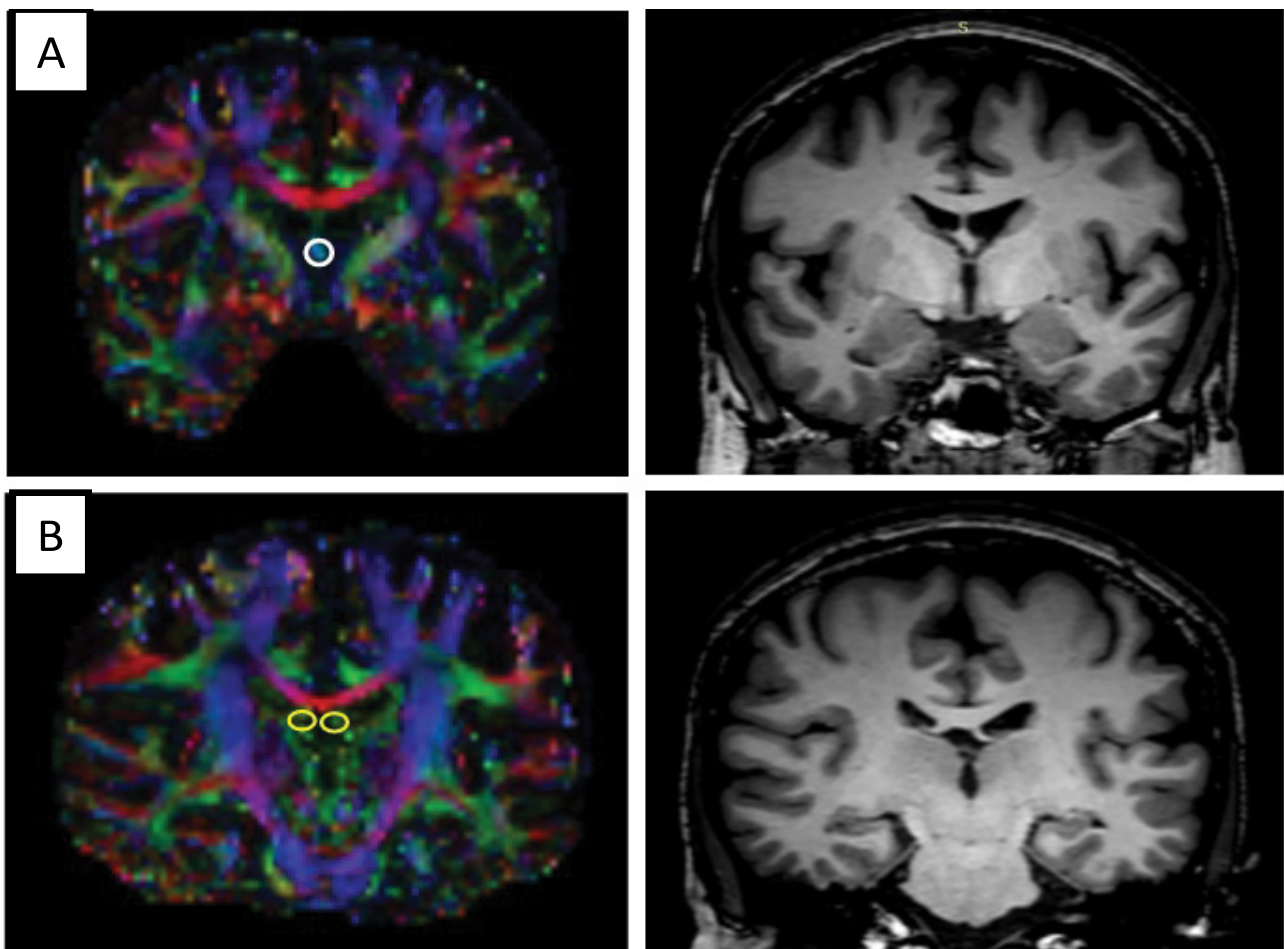| Variable	Cutoff Value	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
Mean FA	0.2467	90	70	75	87.5	80	
	0.2557	80	70	72.7	77.8	75	0.830
	0.2730	70	80	77.8	72.7	75	
Mean ADC	2.1508	100	60	71.4	100	80	
	2.4098	80	70	72.7	77.8	75	0.810
Mean axial diffusivity	2.6708	100	60	71.4	100	80	
	3.0199	80	70	72.7	77.8	75	0.790
Mean radial diffusivity	1.8596	100	60	71.4	100	80	
	2.0230	90	70	75	87.5	70	0.830

Figure 1 Multiple regions of interests (ROI) were selected for diffusion fiber tractography, **(A)** First ROI was placed at fornix crura, **(B)** Second ROI was placed at body part of fornices.
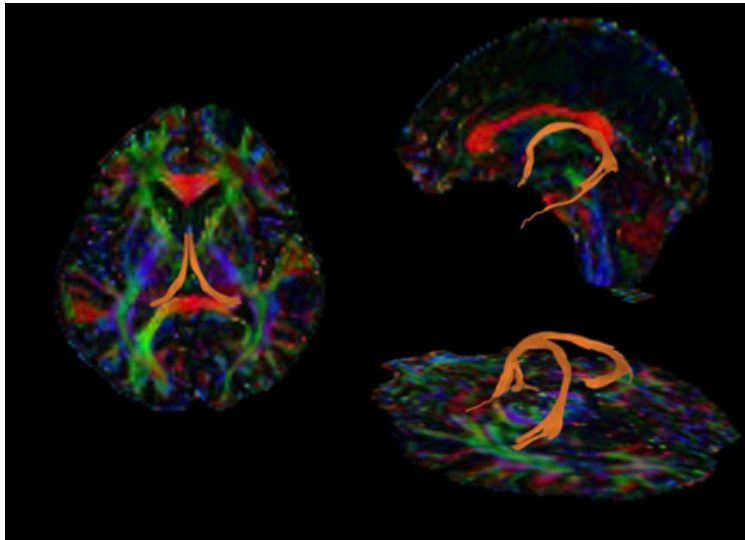
Figure 2   The diffusion fiber tractography of right and left fornices were demonstrated.
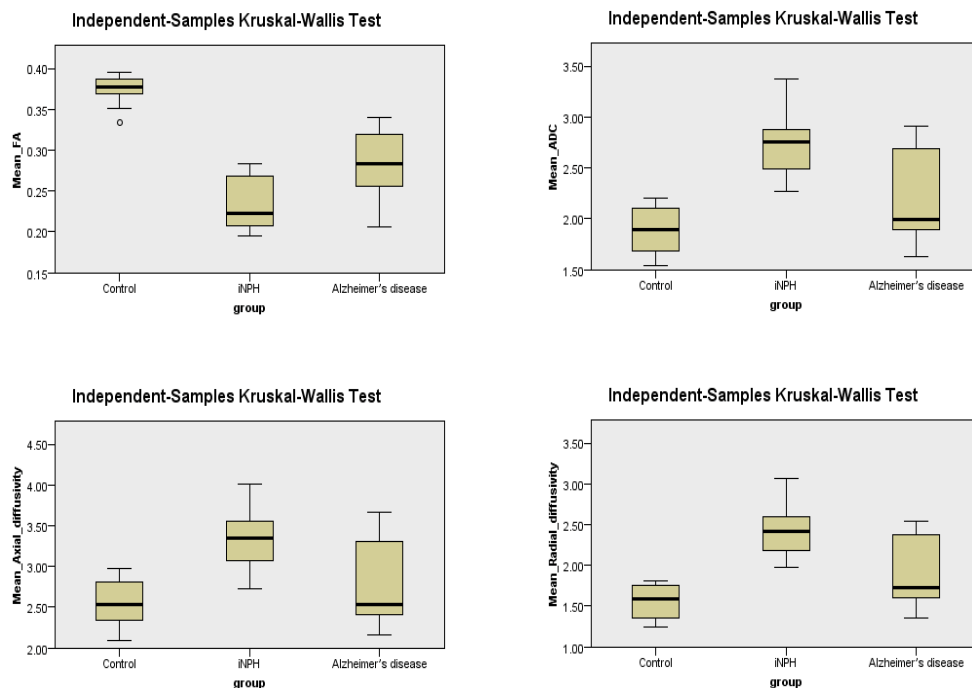

Figure 3   Comparison of DTI parameters of control, iNPH and AD groups by independent-sample Kruskal-Wallis test.

role in the memory function. In this study, we intended to explore microstructural changes in the fornix and the possibility of using DTI parameters as a supportive tool to differentiate AD from iNPH patients.

Many studies have described the microstructural changes in the fornix of AD and mild cognitive impaired patients (MCI) by using various methods of DTI and tractography. However, only a few studies have used DTI techniques to differentiate iNPH and AD patients. Hong et al. [11], revealed a significantly lower mean FA of the hippocampus of AD and iNPH subjects than of normal, healthy, control subjects, and a significantly lower mean FA of the hippocampus of AD than iNPH subjects. Hattori et al. [23], reported a significantly higher FA value and axial eigenvalue of the corticospinal tract for iNPH subjects than for AD and normal control groups. Kim et al. [12], also revealed a significantly higher FA value of the posterior limb of the internal capsule for the iNPH group than the AD and normal control groups. Hattori et al. [24], showed a significantly decreased FA value of the fornix for the iNPH and AD groups than for the normal control group, but there

was no significant difference between the values for the iNPH and AD groups. Furthermore, the antero-posterior directional stretching of the fornix was also described with a significantly lower tract volume for iNPH subjects than for subjects in the AD and normal control groups.

In our study, the lower values for the mean FA of the fornices of iNPH and AD patients than the values of normal control subjects were concordant with a study by Hattori et al. [24]. The decreasing mean FA value of the AD group may be explained by axonal degeneration of the fornix, being the efferent white matter tract from the hippocampus [7]. However, and in contrast with the fall in FA values arising from mechanical compression (as found in the corticospinal tract of iNPH patients, and as reported in previous studies [12,23]), the mean FA values of the fornices of both iNPH and AD patients might reasonably be expected to rise due to the stretching of the fornices resulting from enlarged ventricles. On the other hand, the fornix and the corticospinal tracts are probably inherently different in nature in that the prolonged mechanical pressures on the fornix, caused by enlarged ventricles, likely lead to chronic ischemic changes, axonal loss, interstitial edema or gliosis changes of the fornix fibers, resulting in the decreased FA values described in our study which was in line with previous report [24].

The significantly higher, mean axial diffusivity found among subjects in the iNPH group than in the control group could be explained by the white matter tract stretching. For describing the possible pathogenesis, previous study [23] also revealed increased axial diffusivity in the corticospinal tract which was also stretched in iNPH that could probably described the same mechanism in our finding of increased axial diffusivity in the fornix. As for the AD patients, we assumed that the mean axial diffusivity of the AD group should be lower than that of the control group, but the results revealed a trend of a slightly higher value. This could not be explained by the axonal degeneration mechanism alone.

As the mean radial diffusivity represents myelin integrity [25,26], a higher value for the iNPH and AD groups than for the control group probably demonstrated myelin destruction. Furthermore, a trend of a higher mean radial diffusivity for the iNPH group than for the AD group might be due to a more severe degree of compromised myelin integrity among the iNPH subjects, whereas among the AD patients, demyelination may probably occur after severe axonal loss. However, a previous study of AD-like pathology in mice showed histopathological changes in both the axon and the myelin, yet the DTI parameters demonstrated a significant increase only in the radial diffusivity, with the axial diffusivity still preserved [27]. Therefore, a future human study on AD pathology should be performed for this aspect of imaging-histological correlation.

In order to differentiate iNPH from AD, diagnostic performance, including sensitivity, specificity, PPV and NPV, is demonstrated at **Table 3**. There were equal diagnostic performances when using a mean ADC of 2.1508, or a mean axial diffusivity of 2.6708, or a mean radial diffusivity of 1.8596, as the threshold values, with a diagnostic accuracy of 80%, a sensitivity of 100%, a specificity of

60%, a PPV of 71.4% and an NPV of 100%. When using a mean FA of 0.2467 as the threshold value, the diagnostic accuracy was 80%, with a sensitivity of 90%, a specificity of 70%, a PPV of 75% and an NPV of 87.5%. However, only the mean ADC of the iNPH group was significantly higher than that of the Alzheimer's group (p=0.047).

iNPH is one of the few, treatable causes of dementia. The symptoms of iNPH patients can be improved with surgical placement of a CSF shunt (cerebrospinal fluid shunt), and should not be misinterpreted as due to other causes, such as AD. Therefore, we need a diagnostic tool with high sensitivity and NPV to identify iNPH patients. From our results, the mean ADC is probably the most helpful parameter to discriminate iNPH from AD patients.

Interobserver reliability was excellent in all DTI parameters in our results, may be from the ease to recognize by color changing of the DTI parameter at the ROI. These are helpful because the reproducibility of the DTI method for analysis the fornix can be done with effectiveness.

There were some limitations of the study. The first was its small sample size. The second was the possibility of introducing technical errors or inherent differences in DTI values as a result of using two, different MRI machines, notwithstanding that almost the same DTI protocols were provided by the same vendor. The third limitation was the control group, which was not precisely age-matched with the two diseased groups, and did not undergo full cognitive tests, as did the subjects of the iNPH and AD groups. Another limitation was that we did not evaluate the severity of the diseases and the duration of their symptoms; that may have impacted on the white matter integrity. Finally, some previous research studies examined the DTI parameters by using a different method of post-processing analysis [23,28]; therefore, there are some limitations when making direct comparisons with our results.

Conclusion

Our study revealed different microstructural changes in the fornices of iNPH and Alzheimer's patients evident through differences in their DTI parameters, which probably result from a different pathogenesis of each disease. Overall, our study demonstrated the possibility of using DTI parameters as a supportive tool to discriminate between iNPH and AD patients with high sensitivity and NPV.

Acknowledgements

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