The Evaluation of Posterior Cingulate Gyrus by Diffusion Tensor Imaging in Alzheimer's Disease Patients Compared with Normal Control Subjects

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ABSTRACT

Objective: Posterior cingulate gyrus atrophy is found in early clinical stage of Alzheimer's disease (AD) patients.[1] Diffusion tensor imaging (DTI) can be used for evaluating microstructure change in brain parenchyma.[2] Our objective was to compare the microstructural change at posterior cingulate gyrus between AD patients and normal control subjects by using DTI.

Methods: The retrospective review of 23 AD patients, diagnosed by NINCDS-ADRDA with available MRI data including DTI, and 19 normal control subjects was performed. The DTI parameters of posterior cingulate gyrus of each group were analyzed and compared.

Results: The mean diffusivity (MD), axial diffusivity and radial diffusivity (RD) of posterior cingulate gyrus were significantly increased in AD patients compared with normal control subjects (p value <0.001, <0.001, <0.001, respectively). The fractional anisotropy (FA) was slightly decreased in AD patients compared with normal control subjects but did not reach statistical significance (p value=0.71).

Conclusion: Microstructural change at posterior cingulate gyrus demonstrated by DTI parameters including MD, axial diffusivity and RD were significantly different between AD patients and normal control subjects. These results were probably helpful for early diagnosis, evaluation, and follow up of the AD patients as correlate with clinical findings.

Keywords: Diffusion tensor imaging; Posterior cingulate gyrus; Alzheimer's disease (Siriraj Med J 2019;71: 117-122)

Abbreviations: DTI: Diffusion tensor imaging; FA: Fractional anisotropy; ROI: Region of interest; MD: Mean diffusivity; RD: Radial diffusivity; AD: Alzheimer's disease

INTRODUCTION

Alzheimer's disease (AD) is a major cause of dementia which brings disability to older adults worldwide. Early detection of AD can provide early treatment for this disease and thus delay progression and disability. Many investigations are now emerging to fulfill this purpose such as CSF tau level, genetic test, FDG or amyloid PET. However, AD patients are still diagnosed late in disease course.[1-6]

Furthermore, other causes of dementia such as dementia with Lewy bodies (DLB), frontotemporal dementia (FTD) and idiopathic normal pressure hydrocephalus

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(iNPH) also share common symptoms and signs with AD, but need different specific treatments. A test that can detect AD early and also provide differentiation from other causes will bring many benefits to these patients.[7-9]

The previous study by Pengas et al.,[10] showed that atrophy of posterior cingulate cortex and hippocampus was a feature of early AD. The studies by Minoshima et al., and Nestor et al., also showed hypometabolism in both areas.[11-13]

Diffusion tensor imaging (DTI) is one of the imaging tools for studying microstructural change of white matter which is believed to account for early AD. Previous studies[14-16] demonstrated abnormal FA and MD in posterior cingulate gyrus in AD patients. Our objective was to compare microstructural change at posterior cingulate gyrus between AD patients and normal control subjects by using DTI.

MATERIALS AND METHODS

The study was approved by Siriraj Institutional Review Board (Si 651/2557). Twenty-three AD patients (11 males and 12 females, mean age 78.82 years; range 66-90 years) diagnosed according to NINCDS-ADRDA criteria 2011[17,18,19] with available MRI scan including DTI data were included in the disease group (Table 1). Nineteen normal cognitive subjects (10 males and 9 females, mean age 59.52 years old; range 47-80 years) were enrolled as the control group and recruited from the patients who underwent the MRI study due to non-specific symptoms such as headache or vertigo with normal cognitive function, no abnormal neurological examination and no detectable gross MRI abnormality such as infarction, hemorrhage or mass lesion.

MR Imaging Data Acquisition

MRI acquisitions were done on two machines; the first one was a 3.0 tesla MR system (Archieva, Philips, The Netherlands) with an 8-channel head coil and DTI protocol was a single shot, spin echo EPI; 32 diffusion encoding directions; b value = 0 and 800 s/mm^2; acquisition matrix 112x112; FOV 22.4 cm; voxel size = 2 mm (RL) x 2 mm (AP) with 60 contiguous slices, slice thickness 2.3 mm, and acquisition time was 12:39 min. The other machine was a 3.0 tesla MR system (Ingenia, Philips Medical System, Best, the Netherlands) with 16-channel head coil and DTI protocol was a single shot, spin echo EPI; 32 diffusion encoding directions; b-value = 0 and 800 s/mm^2; acquisition matrix 112x112; FOV 22.4 cm; voxel size = 2 mm (RL) x 2 mm (AP) with 60 contiguous slices, slice thickness = 2.0 mm, and acquisition time was 12:14 min. The 3D-T1 weighted image and fluid-attenuated inversion recovery images were performed in all patients. In AD group, coronal oblique T1W at right angles to the longitudinal axis of the hippocampus was also obtained.

DTI Processing

Processing of the diffusion data including brain extraction and correction for eddy current distortions by using FSL (FMRIB Software Library, version 5.0.8) were done.[20] Then dtifit for local fitting of diffusion tensors was performed. The standard template for ROI measurement (Harvard-Oxford Cortical Structural Atlas) of the posterior cingulate gyrus was placed. Finally, the diffusion tensor parameters including FA, MD, axial diffusivity, and RD were derived and compared between the AD group and control group. (Fig 1)

Statistical analysis

Statistical analysis was performed using PASW (SPSS) version 18. Continuous data analysis was measured and presented as means, standard deviations (SD), min and max parameters. Categorical data analysis was divided by each group and converted into percentage. Sex, education and Scheltens score between AD patients and normal control subjects were compared using Chi-square test. Age at scanning between each group was compared using unpaired t-test.

The diffusion tensor parameters (FA, MD, Axial diffusivity, and RD) were compared between the AD group and control group using Mann-Whitney U test. P-value less than 0.05 was considered statistically significant.

RESULTS

We investigated 23 AD patients (11 males, 12 females, mean age at scanning: 78.8±6.1 years) and 19 normal control subjects (10 males, 9 females, mean age at scanning: 55.0±9.0 years). The age of scan in AD group was higher than that in control group ($p< 0.001$). No gender difference between the two groups ($p= 0.757$) was observed.

Regarding education in AD group, there were 2 patients (8.7%) with no study, 11 patients (47.8%) with primary school graduation, 5 patients (21%) with secondary school graduation and 5 patients (21%) with college degree. The mean age of onset was 77.6±7.0 years and mean TMSE scores (0-30) was 20.83±4 .5 points in AD group.

Scheltens score (range from 0-4 points) in AD group were 2 points in six patients (26.1%), 3 points in fifteen patients (65.2%) and 4 points in two patients (8.7%) whereas the Scheltens score in control group was 1 point

TABLE 1. Shows demographic data as sex, age, TMSE score, education, Scheltens score, age at MRI scanning and underlying diseases of AD patient group.

Number	Sex	Age (years)	TMSE (0-30)	Education	Scheltens score (0-4)	Age at MRI scanning (years)	Underlying diseases
AD1	Male	87	24	Primary school	3	87	DM, HT, DLP
AD2	Female	78	21	Primary school	3	77	DM, HT, DLP
AD3	Male	66	19	Secondary school	3	66	None
AD4	Female	87	22	Primary school	3	87	HT
AD5	Male	82	21	Secondary school	3	82	HT, DLP
AD6	Female	79	25	Primary school	3	79	HT
AD7	Female	84	19	Primary school	3	84	HT, DLP
AD8	Female	90	19	No study	3	90	DM, HT
AD9	Male	83	14	University	3	83	DM
AD10	Male	71	23	No study	2	71	HT, DLP
AD11	Male	72	23	University	2	73	HT, DLP
AD12	Female	80	18	Secondary school	3	81	HT, DLP
AD13	Female	84	21	Primary school	3	84	DM, HT, DLP
AD14	Female	79	26	University	3	79	HT, DLP
AD15	Male	67	22	Secondary school	2	70	DM, HT, DLP
AD16	Male	74	8	Secondary school	2	74	HT, DLP
AD17	Female	76	16	Primary school	3	78	HT, DLP
AD18	Female	81	15	Primary school	4	82	DM, HT
AD19	Female	67	23	Primary school	2	70	HT, DLP
AD20	Female	79	27	Primary school	3	80	HT, DLP
AD21	Male	71	24	Primary school	3	79	HT, DLP
AD22	Male	81	27	University	4	82	None
AD23	Male	68	22	University	2	75	None

Abbreviations: DM=diabetes mellitus, HT=hypertension, DLP= dyslipidemia

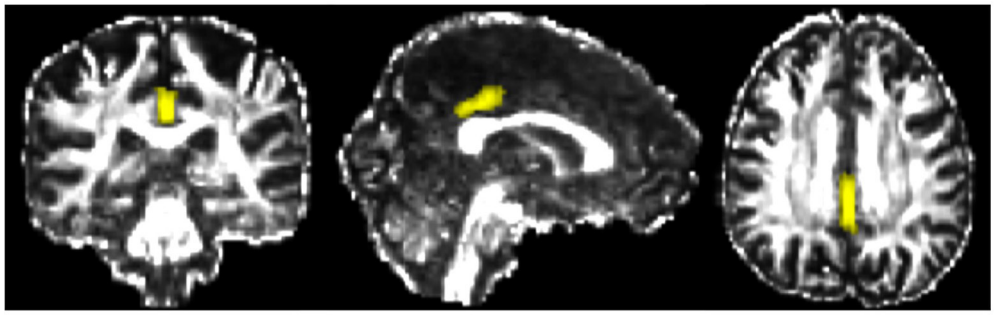

Fig 1. Showed region of interest analysis of the posterior cingulate gyrus demonstrated in axial, sagittal and coronal views in FA map in AD patient.

in eighteen patients (94.7%), and 2 points in one patient (5.3%). Mean Scheltens score in AD group was significantly higher than that in control group ($p < 0.001$). (Table 1)

FA

The mean FA at posterior cingulate gyrus in AD group was slightly lower than that in control group (0.216 ± 0.035 vs 0.218 ± 0.027, respectively). However, there was no statistically significant difference between the two groups (p-value is 0.71). (Table 2)

MD

MD at posterior cingulate gyrus in AD group (1.396 ± 0.195 x 10^{-3} mm^2/s) was statistically significantly higher than that in control group (1.178 ± 0.137 x 10^{-3} mm^2/s), p value <0.001. (Table 2)

Axial diffusivity

Axial diffusivity at posterior cingulate gyrus in AD group (1.659 ± 0.194 x 10^{-3} mm^2/s) was significantly higher than that in control group (1.459 ± 0.263 x 10^{-3} mm^2/s), p value <0.001. (Table 2)

Radial diffusivity (RD)

RD at posterior cingulate gyrus in AD group (1.267 ± 0.200 x 10^{-3} mm^2/s) was significantly higher than that in control group (1.064 ± 0.143 x 10^{-3} mm^2/s), p value <0.001. (Table 2)

TABLE 2. Shows mean FA, mean MD, mean axial diffusivity, and mean RD of AD patients and normal control subjects.

Parameters	AD patients (±SD and range)	Normal control subjects (±SD and range)	P value
Fraction anisotropy (FA)	0.216 ± 0.035 (0.181-0.251)	0.218 ± 0.027 (0.191-0.245)	0.71
Mean diffusivity (MD, 10^{-3} mm^2/s)	1.396 ± 0.195 (1.201-1.591)	1.178 ± 0.137 (1.041-1.315)	<0.0001
Axial diffusivity (AD, 10^{-3} mm^2/s)	1.659 ± 0.194 (1.465-1.853)	1.459 ± 0.263 (1.196-1.722)	<0.0001
Radial diffusivity (RD, 10^{-3} mm^2/s)	1.267 ± 0.200 (1.067-1.467)	1.064 ± 0.143 (0.921-1.207)	<0.0001

DISCUSSION

In early AD, atrophy of hippocampus and posterior cingulate gyrus is a distinct imaging feature.[13] Several studies[10-12] have found that the earliest hypometabolic (F18 FDG-PET) region in AD was the posterior cingulate cortex which showed more significantly decreased metabolism than the mesial temporal structure.

Additional study revealed that there was decreased FA coupled with increased diffusivity (MD) in cingulum fiber which connects the hippocampus and posterior cingulate gyrus reflecting axonal loss or demyelinating process.[16,21-25] Moreover, Salat D et al., revealed that diffusion measurement was related to indices of disease severity and cognitive disability and specifically associated with episodic memory impairment. These findings represented a potential clinical role for DTI to index white matter degeneration and track AD symptoms.[26]

Several previous studies[26-29,31,33] have widely used post-processing analysis software consisting of FSL for DTI analysis at posterior cingulate gyrus. All of these studies supported association of abnormal DTI value at posterior cingulate cortex with early AD. In our study, there was decreased FA with increased mean diffusivity (MD), axial and radial diffusivity in AD patients compared with control subjects. However, only MD, axial diffusivity and RD were significantly statistically different between the two groups. Our result was consistent with the studies by Yoshiura et al., Nakata, et al., and Fellgiebel, et al., which found that increased mean, axial and radial diffusivity in posterior cingulate correlated with AD.

Yoshiura T et al.,[14] found that mean axial and radial diffusivity, but not FA, in the posterior cingulate white matter correlated with MMSE which reflect progression of AD-related histopathological changes. Fellgiebel A et al.,[15]

found significantly decreased FA and increased MD at posterior cingulate white matter in AD compared to normal controls. Nakata Y et al.,[27] found that MD in the posterior cingulum significantly correlated with the MMSE score. However, no significant correlation was seen between FA and MMSE score. The measuring methods were probably different in detail in each study, such as the method of ROI measurement, and also DTI scanning protocol that probably effected the measurement of DTI values.

For correlation with pathophysiology of disease, explanation of the association of increased diffusivity, hypometabolism and atrophy at posterior cingulate gyrus in AD patients was established. MD is a measurement of translational diffusion which increases in the presence of tissue damage.[30] Therefore, MD is expected to increase at the posterior cingulate gyrus in AD patients which indicates pathology in limbic system contributing to memory loss.

In addition, the dissociation between radial diffusivity and axial diffusivity was concordant with the previous study by Song SK et al.,[31-32] which pointed out that significantly increased radial diffusivity reflected myelin injury in AD. However, increased axial diffusivity was not consistent with axonal injury in AD.

In the aspect of FA, there was no significant difference between AD patients and normal control subjects in our study. The FA demonstrated directionality of diffusion and in the white matter, high FA can be found in highly organized tissue with parallel structure. Damage to white matter disrupts the organized structure leading to a decrease in FA. Three decreased FA regions involving medial temporal lobe, temporal lobe proper, and posterior cingulate gyrus were reported to be relatively consistent with AD.[30]

FA in our study was not significantly lower in the AD group which was similar to a study by Yoshiura et al. This can be contributed to rotationally variant during three orthogonal directions measurement of FA. Therefore, the relative orientation of the patient's head concerning the fixed geometry of the MR imaging system gradients can affect FA parameters.[14]

A Study by Nakata et al., in 2008 using tract-specific analysis of posterior cingulate fiber tracts showed significant lower FA in AD patients.[28] However, another study by Nakata et al., in 2009[27] showed no significant correlation between FA and MMSE which used MMSE as an indicator of disease progression in AD. His conclusion suggested that MD in the posterior cingulum is a more sensitive indicator of progression of AD than FA at the posterior cingulum and hippocampal volume.

All of the aforementioned studies reflected the variability of FA and implied that FA is not a reproducible parameter. Thus, factors that can alter FA values are detectable by DTI technique such as parameter, ROI placement,[26,33] voxel size and number of collinear gradients.

Limitations of our study

1. Abnormal DTI findings could be related to other pathology such as dementia other than AD and/or cerebral vascular disease due to non specific in nature of DTI metrics.
2. Mean age at scanning of control group were lower than the AD group. The age-related degeneration of white matter may affect the DTI parameters.

CONCLUSION

The microstructural change at the posterior cingulate gyrus demonstrated by DTI parameters including MD, AD and RD were significantly different between AD patients and normal control subjects. Our findings suggested that DTI parameters including MD, AD and RD at posterior cingulate gyrus are non-invasive markers of AD pathology. Therefore, these are probably helpful for early diagnosis, evaluation, and follow-up of AD patients to correlate with clinical findings. For further studies, advanced imaging techniques that can differentiate between AD and mild cognitive impairment (MCI) will be helpful in clinical practice.

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