Preoperative Diffusion Tensor Imaging Analysis of Optic Radiations: Study in Pituitary Macroadenoma Patients with Optic Chiasm Compression

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Background: *Pituitary macroadenoma with optic nerve or optic chiasm compression may lead to further visual impairment and need surgical treatment.*
Objective: *We aim to evaluate microstructural change of the optic radiation in pituitary macroadenoma patients before surgery compared to the normal control subjects by diffusion tensor imaging (DTI).*
Material and Method: *Nine patients with pituitary macroadenoma and optic chiasm compression confirmed by 3-Tesla MRI (pituitary protocol) and 9 normal control subjects were evaluated with DTI. The probabilistic tractography and DTI parameters of optic radiation were evaluated in both patients and normal control subjects.*
Results: *There were statistically significant increase of radial diffusivity (RD, $p<0.05$), 2nd and 3rd eigen values ($p<0.05$) in pituitary macroadenoma patients whereas, slightly increased in mean diffusivity (MD) and decreased in fractional anisotropy (FA) of the patients but no statistically significant difference ($p = 0.053$ and 0.133, respectively) as compared with normal control subjects.*
Conclusion: *Microstructural change of the optic radiations in pituitary macroadenoma patients with optic chiasm compression was demonstrated by means of DTI parameters before conventional MRI. Therefore, the value of DTI parameters might be non-invasive tools for further evaluation and prediction of visual recovery after surgery as correlate with clinical examination.*

Keywords: *Pituitary macroadenoma, Diffusion tractography, DTI, Optic radiation*

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Pituitary adenoma (PA) is a benign tumor originating in adenohypophyseal cells of the anterior lobe pituitary gland, and classified according to hormonal secretion or size. For hormonal secretion aspect, it is divided to secreting (functioning) PA or non-secreting (non-functioning) PA. When classified by size, it is divided into microadenoma (size ≤1 cm) or macroadenoma (size >1 cm)[1]. Pituitary adenoma causes major symptoms in 2 ways; tumor-related hyper or hypo-secretion of hormone and compression to the surrounding structures[1].

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Visual impairment is one of the common manifestations of pituitary macroadenoma. Visual dysfunction [visual acuity (VA) and visual field (VF) defect] is a main indication for decompressive surgery for the optic fibers[2,3].

Transsphenoidal surgery for pituitary macroadenoma results in a progressive recovery of VF in 95% of patients. The extent of the VF recovery is mainly dependent on the preoperative VF deficit, which emphasize the need for early intervention in these patients[3].

MRI shows a role to evaluate visual impairment in pituitary macroadenoma patient. Hyperintensity on T2W of the optic nerves ventral to the pituitary macroadenoma was associated with visual impairment[4]. However, optic nerve hyperintensity is

usually evaluated by only visual analysis.

Recently, advanced MRI technique such as diffusion tensor imaging (DTI) has been non-invasive technique in studying of integrity of cerebral white matter and tracts, which measures and quantifies tissue microstructural change in terms of diffusion parameters, providing the possibility for the early detection of visual pathway lesions[5].

Ihsan Anik et al, in 2011, used DTI to assess the affected side of optic nerve by measuring fractional anisotropy (FA) and mean diffusivity (MD) values, which might help to estimate the response of visual improvement to the surgical therapy of pituitary macroadenoma in the early postoperative period (2nd day and 6th month)[6].

There is some limitation to evaluate DTI parameters of optic nerve or optic chiasm due to difficulty in directly drawing region of interest (ROI) on the severe optic compression by the large tumor. Up to now, and there were few studies about the optic radiation.

Tobias Engelhorn, et al., in 2012, studied changes in radial diffusivity (RD) and fractional anisotropy (FA) in optic nerve and optic radiation in glaucoma patients and found that the RD increased and FA decreased correlating with established ophthalmological examinations[7].

Therefore, the objective of this study was to evaluate microstructural change demonstrated by means of DTI parameters of optic radiations, evaluation between preoperative pituitary macroadenoma patients as compared with normal control subjects.

Material and Method

Study designs and subjects

This was a prospective single-center study performed at a 3,000-bed university hospital in central Thailand. The study was approved by the institutional review board. The patients with pituitary mass possible macroadema and undergoing pre-operative MRI scan (pituitary protocol) at our institution between May 2015 through October 2015 were recruited. The visual function tests including visual acuity or visual field were performed by an ophthalmologist before surgery. Eligible subjects with contraindication for MRI study, brain pathology within areas of optic radiation, such as infarction, hemorrhage, infection, demyelinating process, space occupying lesion, etc., were excluded from the study.

The inclusion criteria for normal control subjects was patients without history of visual impairment. With the same reason, eligible normal control subjects with brain pathology within areas of optic radiation, such as infarction, hemorrhage, infection, demyelinating process, space occupying lesion, etc., were excluded from the study.

MRI techniques

Imaging was performed on a 3.0-Tesla MRI (Ingenia, Philips, Netherlands). The 32-channel head coils were used for reception of the signal. The conventional MRI of pituitary gland included high resolution (thickness 3 mm, FOV 16x16 cm) in sagittal T1W, coronal T1W and T2W, followed by dynamic contrast enhancement in coronal and post-contrasted image in sagittal and coronal views. The conventional brain imagings were performed in axial T2W and post-contrast T1W with fat suppression. The DTI study was performed with 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 x 2 mm in 70 contiguous slices with slice thickness of 2 mm; TR = 10,424 ms; TE = 104 ms; and flip angle = 90°. Acquisition time was 12: 09 minutes.

Data processing

Probabilistic tractography was performed by using FSL (FMRIB Software Library v.5.0.8)[8]. The diffusion raw data was obtained including DICOM file, b-value (contains scalar value) and b-vector (contains gradient direction) following by eddy currents correction, fitting diffusion tensors (DTIFIT) to obtain scalar DTI maps, and fiber orientation information and Bedpostx-output were done for probabilistic tractography. Each optic radiation tractography was performed by seeding ROI from lateral geniculate nucleus (LGN) mask and terminating at V1 cortex (primary visual cortex) mask which created from standard space (Juelich Histological Atlas). Exclusion mask was used to exclude non-optic radiation fiber. The DTI parameters (FA, MD, $\lambda 1$, $\lambda 2$, $\lambda 3$ and RD) of bilateral optic radiations in patients and normal control subjects were obtained and then the mean values of each side were analyzed (Fig. 1 and 2).

Statistical analysis

The DTI parameters were displayed as the means $\pm$ standard deviation (SD). A 2-sided *p*-value of less than or equal to 0.05 was considered as a statistical significance in comparison of means between patients

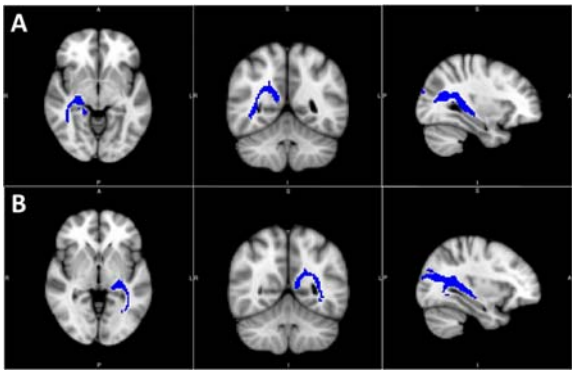

Fig. 1 Bilateral optic radiations from DTI in a 54-year-old man normal control subject: (A) (upper row) right optic radiation in axial, coronal and sagittal views; (B) (lower row) left optic radiation in axial, coronal and sagittal views.

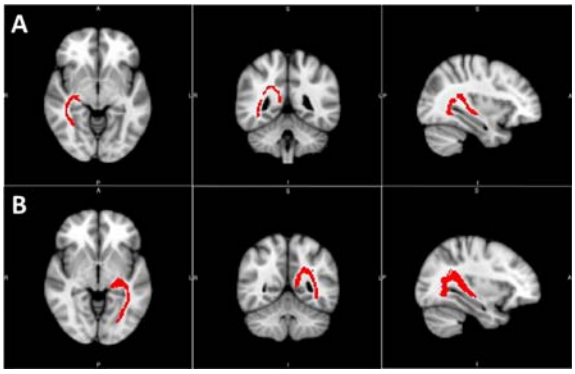

Fig. 2 Bilateral optic radiations from DTI in a 63-year-old man with pituitary macroadenoma with evidence of optic chiasm compression: (A) (upper row) right optic radiation in axial, coronal and sagittal views; (B) (lower row) left optic radiation in axial, coronal and sagittal views.

and control group. The statistical analysis was performed by using SPSS version 21 (SPSS Inc, Chicago, Illinois, United States).

Results

Subjects

Based on the aforementioned inclusion and exclusion criteria, 9 pituitary macroadenoma patients and 9 normal control subjects were recruited. There were 5 males and 4 females in patient group with the mean age of 60 years old (range 43 to 85 years old) (Table 1 and 2). The visual function test was performed at 1 day to 4 months interval time from MRI study.

Nine-normal control subjects had been referred for MRI brain for many reasons without any visual impairment. They were 5 males and 4 females with the mean age of 58.6 years old (range 52 to 67 years old) (Table 1 and 2).

DTI assessment of bilateral optic radiations

There was a statistically significant increase in radial diffusivity (RD) of the patient group compared to the normal control (RD = $0.82\pm0.12 \times 10^{-3}$ mm^2/s vs. $0.70\pm0.04 \times 10^{-3}$ mm^2/s, *p*-value = 0.036). The mean diffusivity (MD) in patient group was increased (MD = $1.02\pm0.14 \times 10^{-3}$ mm^2/s vs. $0.91\pm0.05 \times 10^{-3}$ mm^2/s, *p*-value = 0.053) and fractional anisotropy (FA) was decreased compared to the normal control subjects (FA = 0.39 ± 0.05 vs. 0.42 ± 0.03, *p*-value = 0.13), but no statistical significance. Also a tendency of increased first eigenvalue in patient group was observed, but not significant (Table 3).

Discussion

The pituitary macroadenoma with optic chiasm or optic nerve compression can cause visual abnormality. In some patients, the optic chiasm or optic nerve can be obliterated or cannot be clearly defined due to marked compression from the large pituitary macroadenoma, therefore direct DTI evaluation at the optic chiasm or optic nerve in these patients as correlate with visual abnormality cannot be performed. The optic radiation is the visual pathway that connected from optic chiasm and optic tracts with originating at lateral geniculate nucleus and terminating at primary visual cortex. Therefore, evaluation of microstructural changes at the optic radiation with DTI probably represents early visual pathway abnormality.

This study was designed to explore the microstructural change of optic radiations in pituitary macroadenoma patient with optic chiasm compression compared to the normal control subject. The authors found that, significant increase in radial diffusivity (RD), second eigenvalue and third eigenvalue compared to the normal control subject could be explained that compression to optic pathway before synapsing with third order neurons in lateral geniculate bodies might cause microstructural change possibly myelin damage or glia cell impairment of optic radiation detected early with the sensitive tool (diffusion tensor imaging, DTI) before the gross structural change seen on conventional MRI, such as T2W or T2W/FLAIR sequences.

Considering the RD value of each patient, the authors found that, 2 patients had the highest RD values (about 1.0×10^{-3} mm^2/s, mean RD of normal

Table 1. Demographic data of the normal control and pituitary macroadenoma patient groups

Groups	No. of Subjects	Male	Female	Mean age (years)	Age range (years)
Control	9	5 (55.6%)	4 (44.4%)	58.6	52 to 67
Patient	9	5 (55.6%)	4 (44.4%)	60	43 to 85

Table 2. Demographic data each of patients with pituitary macroadenoma patients

No.	Sex	Age (years)	Postoperative		RD (x 10^{-3}) mm^2/s	Comment
			Visual acuity	Visual field		
1	F	51	Improve	No defect	0.67675	-
2	M	67	Worsen	-	1.0045	No post operative VF
3	M	47	Improve	Improve	0.7695	-
4	F	55	No defect	Improve	0.85075	-
5	M	80	Improve	Not improve	0.795	-
6	M	55	-	-	0.746	No data VA, VF
7	F	43	Improve	No defect	0.70075	-
8	M	85	-	-	1.0771	No data VA, VF
9	F	57	No defect	No defect	0.71875	-

Table 3. Mean DTI parameters bilateral optic radiations of normal control and the pituitary macroadenoma patient groups, displayed in means $\pm$ standard deviation (SD)

DTI parameters	Control	Patient	*p*-value
FA	0.42$\pm$0.03	0.39$\pm$0.05	0.133
MD (mm^2/s)	0.91$\pm$0.05	1.02$\pm$0.14	0.053
$\lambda1$ (mm^2/s)	1.35$\pm$0.04	1.42$\pm$0.15	0.197
$\lambda2$ (mm^2/s)	0.82$\pm$0.04	0.95$\pm$0.14	0.032*
$\lambda3$ (mm^2/s)	0.57$\pm$0.04	0.69$\pm$0.14	0.041*
RD (mm^2/s)	0.70$\pm$0.04	0.82$\pm$0.14	0.036*

* Indicates statistical significance; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity [($\lambda2 + \lambda3$)/2]; $\lambda1$, 1st eigenvalue; $\lambda2$, 2nd eigenvalue; $\lambda3$, 3rd eigenvalue; MD, $\lambda1$, $\lambda2$, $\lambda3$, RD values x 10^{-3}

control subject about 0.70$\pm$0.04 x 10^{-3} mm^2/s). One of these had worsening of visual acuity after surgery. This may be presumed that pre-operative RD value might be predictive indicator for post-operative visual recovery. Unfortunately, this patient also had post-operative bleeding complication which might interfere evaluating visual function recovery. The other patient had no pre or post-operative visual function assessment.

The increased MD in patient group implied loss of cellularity or edema along the optic radiation, though no statistical significance.

Through no statistical significance of the difference of FA values between patients and normal group, a trend to slightly decreased FA in patient group was found in this study. This was probably from some degree of axonal abnormality insulted from the compressive optic chiasm. However, the value of the FA parameter for evaluating specific microstructural change in the optic radiation in this situation need to be more explored.

In previous study, they found age-related RD and FA change, which increased RD and decreased FA related to increasing age[9,10]. According to this study, age-related parameter changes might have minor effect to the results due to rather age-match control subjects.

The DTI studies of the optic radiation in other diseases, such as glaucoma[7] demonstrated changes of RD and FA in the same way as this study. Both

conditions (glaucoma and optic compression by pituitary tumor) might be probably assumed to affect optic radiation or distal optic pathway with the same mechanism of neurodegeneration along the distal nerve fiber. In glaucoma study, they mentioned that the possible false positive resulted from change of direction of the optic pathway at the synaptic point of the lateral geniculate body, which was still inconclusive up to current knowledge. The change of neurodegeneration was also demonstrated in many other neurodegenerative diseases including Alzheimer's disease[11] which has abnormality along memory pathway and myelin damage has been proposed to be the early abnormality.

However, this study did not demonstrate directly the pathology or mechanism of DTI parameter changes on the posterior optic pathway. Further study with post operative DTI of optic radiation is mandatory to clarify the possible mechanism.

Limitations of our study were relative small sample size, incomplete post operative visual assessment data, no comparable post operative MRI to evaluate changes of DTI parameter corresponding with visual function assessment.

Conclusion

Among pituitary macroadenoma patients with optic chiasm compression, which is probably explained by neuronal degeneration along the optic pathway distally, showed significantly increased radial diffusivity (RD) of bilateral optic radiations which probably representing microstructural change with myelin damage and be able to be early detected before gross structural change on conventional MRI study. Therefore, the value of DTI parameters needs to be more explored and might be non-invasive tools for further evaluation and prediction of visual recovery after surgery as correlate with clinical examination.

What is already known from this topic?

DTI can demonstrate microstructural change in brain white matter fiber. The pituitary macroadenoma with optic chiasm compression can cause visual loss. However, DTI study with probabilistic method of fiber tractography of optic radiation is not well evaluated in pituitary macroadenoma patients.

What this study adds?

DTI parameters evaluated from probabilistic method of fiber tractography of optic radiation can demonstrate white matter fiber abnormality in pituitary macroadenoma patients before surgery as compared with normal control subject. The value of DTI parameters needs to be more explored and might be non-invasive tools for further evaluation and prediction of visual recovery after surgery as correlate with clinical examination.

Potential conflicts of interest

None.

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การวิเคราะห์ใยประสาทตาส่วนออพติคเรดิเอชั่นก่อนผ่าตัดโดยการตรวจภาพเอ็มอาร์ไอดิฟฟิวชั่น เทนเซอร์: การศึกษาในผู้ป่วยเนื้องอกต่อมใต้สมองที่มีการกดเบียดเส้นประสาทตา ส่วนออพติคไคแอสซัม

ชนน งามสมบัติ, ดุลยพร วงศ์แสวง, อติพร ตวงทอง, นพศักดิ์ ผาสุขกิจวัฒนา, สุภเลิศ ประคุณหังสิต, ธีรพล วิทธิเวช, บรรพต สิทธินามสุวรรณ, พนิดา ชาญเชาว์วานิช, จารุวรรณ เวียนขนาน, อรสา ชวาลภาฤทธิ์

ภูมิหลัง: *เนื้องอกต่อมใต้สมองที่มีภาวะกดทับของเส้นใยประสาทตา สามารถทำให้เกิดการมองเห็นที่ลดลงผิดปกติและอาจจำเป็นต้องได้รับการผ่าตัด เอ็มอาร์ไอดิฟฟิวชั่นเทนเซอร์เป็นเทคนิคการตรวจที่สามารถประเมินคุณภาพของเส้นใยประสาทได้*

วัตถุประสงค์: *การศึกษานี้ต้องการประเมินการเปลี่ยนแปลงของเส้นใยประสาทตาส่วนออพติคเรดิเอชั่นในผู้ป่วยเนื้องอกต่อมใต้สมอง ที่มีการกดทับใยประสาทตาโดยใช้เอ็มอาร์ไอดิฟฟิวชั่นเทนเซอร์เปรียบเทียบกับกลุ่มประชากรปกติ*

วัสดุและวิธีการ: *ภาพการตรวจเอ็มอาร์ไอดิฟฟิวชั่นเทนเซอร์ของผู้ป่วยเนื้องอกต่อมใต้สมองที่มีการกดทับใยประสาทตา 9 รายกับกลุ่มประชากรปกติ 9 ราย จะถูกนำมาวิเคราะห์เปรียบเทียบความแตกต่างของค่าดิฟฟิวชั่นเทนเซอร์ในเส้นใยประสาทตาส่วนออพติคเรดิเอชั่น*

ผลการศึกษา: *พบมีการเพิ่มขึ้นของค่าการแพร่ของน้ำในแนวตั้งฉากกับแกนหลักของใยประสาทส่วนออพติคเรดิเอชั่น อย่างมีนัยสำคัญทางสถิติของกลุ่มผู้ป่วย เมื่อเทียบกับกลุ่มประชากรปกติ ในขณะที่ค่าการแพร่เฉลี่ยของน้ำในใยประสาทเพิ่มขึ้นเล็กน้อยและค่าการแพร่โดยรวมมีการลดลงเล็กน้อยในกลุ่มผู้ป่วย แต่ไม่พบความแตกต่าง อย่างมีนัยสำคัญทางสถิติกับกลุ่มประชากรปกติ*

สรุป: *การเปลี่ยนแปลงของเส้นใยประสาทตาส่วนออพติคเรดิเอชั่นของผู้ป่วยเนื้องอกต่อมใต้สมอง ที่มีการกดทับใยประสาทตาสามารถตรวจพบแสดงได้โดยเอ็มอาร์ไอดิฟฟิวชั่นเทนเซอร์ โดยเชื่อว่าอาจจะเป็นการตรวจที่ช่วยประเมินก่อนการผ่าตัดรวมถึงอาจช่วยคาดการณ์ความสามารถในการมองเห็นหลังผ่าตัดในผู้ป่วยเนื้องอกต่อมใต้สมองที่มีการกดทับใยประสาทตาได้ ถ้ามีการศึกษาเปรียบเทียบกับการตรวจการมองเห็นทางคลินิคอย่างละเอียดในอนาคต*