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Original Article

Factors Influencing Visual Field Recovery after Transsphenoidal Resection of a Pituitary Adenoma

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Purpose: This study aimed to analyze the factors influencing visual field recovery after transsphenoidal approach-tumor resection (TSA-TR) in pituitary adenoma patients with visual field defects (VFDs).

Methods: We retrospectively evaluated 102 eyes of 102 patients with VFDs induced by pituitary adenomas who underwent TSA-TR between January 2010 and December 2015. All patients had been observed for more than one year. The severity of the VFD in each patient was evaluated using the mean deviation (MD) and pattern standard deviation in the most-affected eye. Clinical and demographic data such as preoperative visual acuity and visual field, age, sex, tumor volume, neurological symptoms at diagnosis, duration of symptoms, patterns of the preoperative VFD, and preoperative central VFD were investigated and analyzed for association with recovery of the visual field.

Results: Recovery from VFDs occurred in 71 (69.6%) eyes after a mean period of 18.36 ± 5.21 months. The recovery group was younger (p = 0.003), had higher preoperative MD values (p = 0.016), and had better preoperative visual acuity (p = 0.03), compared with the non-recovery group. Preoperative central VFD (p = 0.006) and preoperative bilateral VFD (p = 0.016) were significantly less frequent in the recovery group. Multivariate logistic regression revealed that age at diagnosis (odds ratio [OR], 0.962; p = 0.022), preoperative MD (OR, 1.069; p = 0.046), preoperative central VFD (OR, 0.212; p = 0.039), and preoperative bilateral VFD (OR, 0.212; p = 0.035) were associated with visual field recovery after TSA-TR.

Conclusions: Younger age, higher preoperative MD, and the preoperative abscence of central VFD or bilateral VFD were favorable factors influencing visual field recovery after TSA-TR in patients with pituitary adenomas. An understanding of the associated clinical factors may help predict visual outcomes after TSA-TR in pituitary adenoma patients with VFDs.

Key Words: Influencing factors, Pituitary neoplasms, Visual fields

Pituitary tumors account for approximately 15% of all brain tumors, and the growing tumors press against the optic chiasm, resulting in impairment of visual function manifested as visual field defects, decreased visual acuity, and decreased color vision [1]. As the tumors continue to grow, they impair visual function by pressing on the anterior visual pathway. In addition to impairing visual function, neurological symptoms such as headache, vomiting, dizziness, and diplopia, may occur, because the cavernous sinus, internal carotid artery, and cranial nerves III, IV, and VI

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anatomically surround the pituitary gland. However, among these neurological symptoms, visual symptoms, such as decreased visual acuity or visual field defect, have been found to occur most frequently [2]. Pituitary adenoma is the most common benign tumor of the central nervous system that can affect the optic chiasm, and the frequency of accompanying visual field defects has been reported at approximately 10% to 30% [3-5]. These accompanying visual field defects are recognized as one of the primary indications for surgery on pituitary tumors.

Transsphenoidal surgery has been reported to safely reduce the pressure on the anterior visual pathway in most patients [6]. However, it is important to predict an accurate postoperative prognosis because effective decompression by transsphenoidal surgery does not necessarily restore optic nerve function. Recently, efforts have been made to evaluate the correlation between postoperative prognosis and various clinical symptoms. Previous studies have reported age, tumor size, preoperative degree of visual field defect and visual acuity, preoperative period of symptoms, and thickness of the layer of the optic nerve fiber as factors related to the prognosis of postoperative visual field, but results vary and are at times conflicting [7-10]. Further, reports from Korea are limited. Hence, the present study was designed to evaluate factors associated with postoperative recovery of the visual field in patients with pituitary adenoma after transsphenoidal surgery.

Materials and Methods

The medical records of 388 patients who underwent transsphenoidal approach-tumor resection (TSA-TR) after being diagnosed with a pituitary adenoma at Chonnam National University Hospital between January 2010 and December 2015 were retrospectively analyzed. Among them, 102 eyes of 102 patients who satisfied the inclusion criteria for this study were investigated. The study protocol was approved by the institutional review board of Chonnam National University Hospital (TMP-2017-248) and followed the tenets of the Declaration of Helsinki. This study was retrospective, and the informed consent on subject was waived.

The inclusion criteria were as follows: a compressive lesion of the optic chiasm confirmed by head magnetic resonance imaging (MRI), first transsphenoidal surgery, or visual field defect found in the preoperative visual field examination. The presence of a visual field defect was determined by a mean deviation (MD) or pattern standard deviation value out of the normal range during visual field examination using a Humphrey Visual Field Analyzer (Carl Zeiss Meditec, Dublin, CA, USA). The exclusion criteria for this analysis were as follows: past history of previous treatment such as radiotherapy or chemotherapy; presence of any ophthalmological symptom other than optic nerve compression symptoms caused by the tumor; recurrence or other complications after transsphenoidal surgery; radiotherapy or other anticancer treatment administered postoperatively; or any other history of neurologic disease leading to a visual field abnormality. Only those patients who met the inclusion criteria and had been followed for at least one year were included. The eye with the worse visual field defect from each patient was selected for analysis.

All subjects underwent ophthalmological examination and head MRI during the period three months before and after surgery. For preoperative ophthalmological examinations, slit lamp biomicroscopy, Goldmann applanation tonometry, and fundus photography were used to exclude ophthalmological diseases that may have affected visual acuity and the visual field, such as cataracts, glaucoma, and retinal detachment. Abnormal vision and visual field defects were evaluated using a visual acuity test and automatic visual field test. For the automatic visual field test, the 30-2 Swedish interactive threshold algorithm of the Humphrey Visual Field Analyzer II was used. Only data that satisfied the reliability criteria were analyzed in the visual field examination results, including fixation losses less than 20%, false-negative error less than 20%, and false-positive error less than 20%.

Patients who were found to have visual field defects in the visual field examinations received follow-up at 6-month intervals. Judgment of recovery was made at the last follow-up observation. Recovery of visual field defects was defined as reduction in the absolute value of MD of 1 dB or more at the postoperative visual field examination compared with the preoperative examination. Visual fields needed to improve more than 1 dB at least 2 consecutive times for us to count the test results as improved, in order to prevent the error of decibel change from fluctuations outside of recovery from the disease. Patterns of binocular visual field defects were also determined. Bilateral classification included bitemporal, homonymous, anterior junc-

tional (generalized depression with contralateral temporal defect), generalized field depression and unilateral [11]. To classify as quadrantanopia, a minimum of three non-edge points had to be involved at the 1% level or lower on the pattern deviation plot. The defect also had to respect the vertical meridian. Defects extending past a single quadrant were classified as hemianopia. Superior and inferior field defects in the nerve fiber layer distribution were classified as altitudinal. In the eyes included in the analysis, the presence of a central visual field defect was determined, based on the definition of "a visual field defect within 10° of fixation with at least one point at P <1% lying at the four innermost central points." [12].

Head MRI confirmed the compressive lesion of the optic chiasm before surgery, and the largest length among (a) horizontal lengths (cm) and (b) vertical lengths (cm) of the tumors on the coronal plane and the largest length among (c) front and back lengths of the tumors on the sagittal plane were measured. The volume of the pituitary tumor was calculated by the following formula:

$$\text{Volume} = 4/3\ \pi \times \frac{(a)}{2} \times \frac{(b)}{2} \times \frac{(c)}{2}\ \text{cm}^3$$

Pituitary adenomas are classified as functional or non-functional adenomas depending on their hormonal activity. In functional adenomas, the various types of hormone-secreting tumor cells were identified on histologic examination. We confirmed the classification of functional or non-functional adenoma by pathologic diagnosis in medical records.

In addition, information about clinical and demographic characteristics such as age, sex, medical history, preoperative neurological symptoms, and the period from symptom onset to surgery was obtained through medical records for patients satisfying the inclusion criteria.

The statistical analysis was conducted using PASW Statistics ver. 18.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics for all patients were calculated for age, sex, visual acuity (logarithm of the minimum angle of resolution, logMAR), period from neurological symptom onset to surgery, volume of the pituitary adenoma, neurological symptoms, pattern of visual field defect, and the presence of a central visual field defect. Among patients who received TSA-TR, the group exhibiting visual field recovery after surgery and the group that did not recover were compared using a *t*-test or chi-square test. Univariate analysis was conducted for each variable to analyze factors related to postoperative recovery of the visual field, and multivariate logistic regression analysis was conducted for factors with a *p*-value smaller than 0.10 in the univariate analysis. Statistical significance was defined as a *p*-value smaller than 0.05.

Results

The mean patient age was 55.55 ± 15.84, and there were 58 men and 44 women. The mean MD was -11.10 ± 9.15 dB and the mean visual acuity was 0.34 ± 0.60 logMAR in the preoperative visual field examination. The mean period from neurological symptom onset to surgery was 222.65 ± 302.29 days and the preoperative mean tumor volume was 17.81 ± 19.07 cm^3. Among the pituitary adenomas included in this study, there were 84 nonfunctioning pituitary adenomas (82.35%) and 18 functioning pituitary adenomas (17.65%). In terms of neurological symptoms, 54 patients had visual symptoms such as decreased visual acuity or visual field defect (52.94%), which constituted the majority,

Table 1. Baseline patient characteristics

Variable	Value
Age (yr)	55.55 ± 15.84
Sex (male / female)	58 / 44
Initial BCVA (logMAR)	0.342 ± 0.60
Last BCVA (logMAR)	0.219 ± 0.56
Mean deviation (dB)	-11.10 ± 9.15
Pattern standard deviation (dB)	7.61 ± 5.56
Duration of symptoms (day)	222.65 ± 302.29
Tumor volume (cm^3)	17.81 ± 19.07
Pathology	
Non-functioning pituitary adenoma	84 (82.35)
Functioning pituitary adenoma	18 (17.65)
Neurologic symptom at diagnosis	
Visual symptom	54 (52.94)
Headache	28 (27.45)
Dizziness	8 (7.84)
Asymptomatic diagnosis	12 (11.76)

Values are presented as mean ± standard deviation, number, or number (%).
BCVA = best-corrected visual acuity; logMAR = logarithm of the minimum angle of resolution.

followed by 28 patients with headache (27.45%), and 8 patients with dizziness (7.84%). Twelve patients did not have any subjective neurologic symptoms (11.76%) (Table 1).

The patterns of visual field defects of the included patients are presented in Table 2. Among the patients, 60 had unilateral visual field defects (58.82%). The subject with the homonymous field defect was absent from the group. In terms of the visual field defect pattern of the most-affected eye, 43 patients had temporal hemianopsia (42.2%), which was most common, followed by 28 patients with temporal quadrantanopia (27.5%), 14 with altitudinal defect (13.7%), and 17 with generalized depression (16.7%) (Table 3).

After follow-up for 18.36 ± 5.21 months, on average, visual field defects showed recovery in 71 eyes (69.61%). The average MD and pattern standard deviation were -6.95 ± 8.49 and 5.78 ± 5.06 dB at the final follow-up visual field examination, respectively. Patients who showed recovery in the visual field examination were younger (p = 0.003), had better preoperative MD (p = 0.016), and better preoperative visual acuity (p = 0.030). Furthermore, subjects in this group had fewer central visual field defects (p = 0.006) and fewer bilateral visual field defects (p = 0.016) in the preoperative visual field examination. The presence of preoperative neurological symptoms (p = 0.479) and the preoperative visual field defect pattern of the most-affected eye (p = 0.091) were not significantly different between the two groups (Table 4).

Multivariate logistic regression analysis revealed that lower patient age (odds ratio, 0.962; p = 0.022), better preoperative MD (odds ratio, 1.069; p = 0.046), absence of central visual field defect (odds ratio, 0.212; p = 0.039), and unilateral visual field defect (odds ratio, 0.212; p = 0.035) were associated with postoperative visual field recovery (Table 5). Fig. 1A-1D and 2A-2D display data from representative cases of pituitary adenoma. Fig. 1 shows a 72-year-old man who exhibited a bilateral visual field defect. Central visual field defect was apparent in the preoperative visual field of the left eye (most-affected eye; MD, -13.99 dB), and a visual field defect of the opposite eye (MD, -6.58 dB) was also evident. There was no visual field recovery in the postoperative visual field at 12 months after transsphenoidal surgery. Fig. 2 depicts results for a 42-year-old woman who exhibited a unilateral visual field defect. There was no central visual field defect in the preoperative visual field of the left eye (MD, -8.00 dB), and there was a normal visual field for the opposite eye (MD, -1.45 dB). There was marked visual field recovery in the postoperative visual field of the left eye at 12 months after transsphenoidal surgery.

Discussion

The presence of a visual field defect is one of the common indications for surgery in patients with pituitary tumors, and the degree of the visual field defect should be identified through a preoperative visual field examination, even if the patient does not complain of symptoms. If the tumor is accompanied by a visual field defect, it is clinically important to predict the prognosis for postoperative visual field recovery. Every study that has analyzed the factors related to prognosis so far has yielded different results. Most previous studies have focused on quantitative factors such as age, tumor volume, and MD value in the preoperative visual field exam. In this study, we further analyzed whether qualitative characteristics such as the existence of neurological symptoms, the range of the visual field defect, and whether the pattern of the visual field defect included a central visual field defect were associated with visual prognosis.

Table 2. Patterns of binocular visual field defects in patients with pituitary adenoma

Type of defect	No. of patients (%)
Unilateral visual field defect	42 (41.18)
Bilateral visual field defect	60 (58.82)
Bitemporal defect	50 (49.01)
Generalized depression with contralateral temporal defect	2 (1.96)
Bilateral generalized field defect	8 (7.84)

Table 3. Patterns of visual field defects of the most-affected eye in patients with pituitary adenoma

Type of defect	No. of patients (%)
Temporal quadrantanopia	28 (27.45)
Temporal hemianopia	43 (42.16)
Altitudinal	14 (13.73)
Generalized depression	17 (16.67)

Table 4. Preoperative characteristics of patient groups according to visual field recovery after trans-sphenoidal resection of pituitary tumors

Variable	Recovery (n = 71)	Nonrecovery (n = 31)	*p*-value
Age (yr)*	49.89 ± 15.05	59.51 ± 14.80	0.003
Male†	37 (52.1)	21 (67.7)	0.193
Preoperative visual acuity (logMAR)*	0.25 ± 0.47	0.58 ± 0.75	0.030
Preoperative visual field			
Mean deviation (dB)*	-9.50 ± 8.12	-14.76 ± 10.40	0.016
Pattern standard deviation (dB)*	23.08 ± 122.27	5.13 ± 5.93	0.389
Duration of symptoms (day)*	232.99 ± 318.15	198.97 ± 265.76	0.604
Follow-up duration(mon)*	24.20 ± 6.22	28.60 ± 7.78	0.681
Tumor volume (cm^3)*	19.05 ± 21.20	14.97 ± 12.84	0.323
Pathology†			1.000
Non-functioning pituitary adenoma	58 / 71 (81.7)	26 / 31 (83.9)	
Functioning pituitary adenoma	13 / 71 (18.3)	5 / 31 (16.1)	
Neurologic symptoms at diagnosis†			0.479
Asymptomatic diagnosis	7 (9.9)	5 (16.1)	
Headache	18 (25.4)	10 (32.3)	
Dizziness	7 (9.9)	1 (3.2)	
Visual symptom	39 (54.9)	15 (48.4)	
Patterns of binocular VFD†			0.016
Unilateral VFD	35 (49.3)	7 (22.6)	
Bilateral VFD	36 (50.7)	24 (77.4)	
Patterns of VFD of more-affected eye†			0.091
Temporal quadrantanopia	23 (32.4)	5 (16.1)	
Temporal hemianopia	31 (43.7)	12 (38.7)	
Altitudinal	9 (12.7)	5 (16.1)	
Generalized depression	8 (11.3)	9 (29.0)	
Presence of central VFD†	42 (59.2)	27 (87.1)	0.006

Values are presented as mean ± standard deviation or number (%).
logMAR = logarithm of the minimum angle of resolution; VFD = visual field defect.
*Student *t*-test; †Pearson's chi-square test.

Tumors that occur in the pituitary gland include pituitary adenoma, craniopharyngioma, and Rathke's cleft cyst, which are usually benign tumors [13]. All patients in this study had pituitary adenoma, including 84 nonfunctioning and 18 functioning pituitary adenomas. The most common neurological symptoms were visual, including decreased visual acuity and decreased visual field (52.94%), followed by headache, no symptoms, and dizziness. Hollenhorst and Younge [4] investigated the visual symptoms of 1,000 patients with pituitary adenoma and found that 70% of them had decreased visual field, accounting for the largest proportion of patients. In a study of 103 patients with pituitary adenoma, Ogra et al. [11] reported that decreased visual acuity accounted for the largest percentage (39%) of initial symptoms, followed by endocrine abnormality at 21%. The results of our study are in line with these results in that visual symptoms were also the most common neurological symptoms.

Ogra et al. [11] further reported that among 54 pituitary adenoma patients with visual field defects, the most frequently encountered defects were bitemporal defects at 41%, followed by unilateral defects, at 33%, and homonymous defects at 13%. In this present study, bitemporal defects were also the most frequent, at 49.1%, but no patients

Table 5. Factors influencing visual field recovery after transsphenoidal resection of pituitary tumors

Variable	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Age (yr)	0.956 (0.926–0.986)	0.005	0.962 (0.931–0.994)	0.022
Male	0.518 (0.214–1.256)	0.146		
Preoperative visual acuity (logMAR)	0.388 (0.171–0.878)	0.023	0.767 (0.244–2.410)	0.650
Preoperative MD (dB)	1.063 (1.015–1.114)	0.010	1.069 (0.996–1.148)	0.046
Preoperative PSD (dB)	1.003 (0.990–1.016)	0.659		
Tumor volume (cm^3)	1.013 (0.987–1.041)	0.326		
Duration of symptoms (day)	1.000 (0.999–1.002)	0.600		
Neurologic symptoms at a diagnosis		0.507		
Asymptomatic diagnosis	Reference			
Headache	1.286 (0.322–5.130)	0.722		
Dizziness	5.000 (0.459–54.513)	0.187		
Visual symptom	1.857 (0.510–6.766)	0.348		
Patterns of VFD in most-affected eye		0.108		
Temporal quadrantanopia	Reference			0.701
Temporal hemianopia	0.562 (0.174–1.818)	0.336	0.712 (0.155–3.273)	0.663
Altitudinal	0.391 (0.091–1.684)	0.208	0.657 (0.105–4.127)	0.654
Generalized depression	0.193 (0.050–0.751)	0.018	0.249 (0.023–2.702)	0.253
Presence of bilateral VFD	0.300 (0.115–0.785)	0.014	0.212 (0.050–0.896)	0.035
Presence of central VFD	0.215 (0.068–0.679)	0.009	0.212 (0.049–0.927)	0.039

CI = confidence interval; logMAR = logarithm of the minimum angle of resolution; MD = mean deviation; PSD = pattern standard deviation; VFD = visual field defect.

had homonymous defects. For a homonymous defect to appear, the lesion must be located in the optic tract, which is farther back from the optic chiasm, or the compression effect of the tumor must act on the optic tract. The absence of homonymous defects in our study may be due to the location of most adenomas at the optic chiasm.

In a retrospective study of 73 patients, Barzaghi et al. [14] noted that the significant factors for complete recovery of the visual field after pituitary adenoma surgery included better MD before surgery, lower patient age, and small tumor diameter. The researchers reported that neither sex nor the period from symptom onset to surgery were associated with postoperative prognosis. In a retrospective study of 57 patients, Lee et al. [9] found that high pressure caused by a tumor visible on MRI, severe visual field defect before surgery, and a thin inferior retinal nerve fiber layer as seen in preoperative optical coherence tomography were associated with poor postoperative visual function and can be used as predictive variables. In agreement with previous reports, the present study found that lower patient age and better preoperative MD were associated with visual field recovery after surgery. Furthermore, in this study, the presence of central visual field defects and bilateral visual field defects were found to be associated with poor prognosis, which is a meaningful result.

The worse the preoperative MD, the more likely there will be bilateral visual field defects. However, when reviewing each patient's visual field examination, we found many patients who had bilateral visual field defects and relatively good preoperative MD values. Conversely, even if the preoperative MD values are severe, the opposite visual field could be preserved. Because of the nature of the study, only the eye with the worse MD value was included as a preoperative value, so the preoperative MD of the contralateral eye was not considered. When we analyzed them as separate factors, we found that preoperative MD, bilateral visual field defects, and central visual field defects were independently associated with visual outcome after

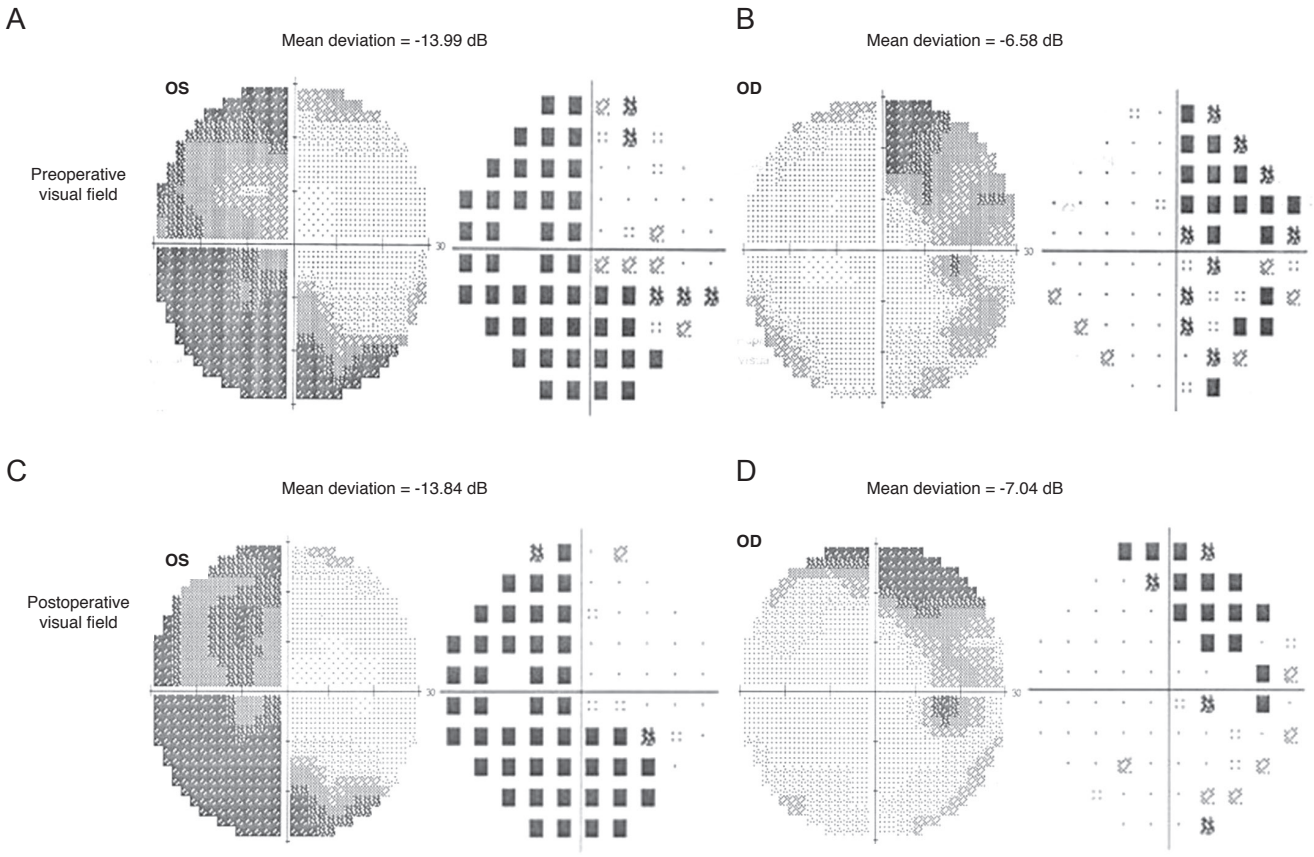

Fig. 1. A 72-year-old man who was diagnosed with pituitary adenoma and underwent transsphenoidal surgery. (A) Central visual field defect is apparent in the preoperative visual field of the left eye (OS; mean deviation, -13.99 dB), (B) as is visual field defect of the opposite eye (mean deviation, -6.58 dB). (C,D) There was no visual field recovery in the postoperative visual field at 12 months after transsphenoidal surgery. OD = right eye.

trans-sphenoidal resection of pituitary tumors. Likewise, it seems that the patients with a central visual field defect might have lower preoperative visual acuity, but the relationship is not absolute.

Yu et al. [7] claimed that small preoperative tumor volume was an independent factor in visual field recovery after TSA-TR of pituitary adenoma, but in the present study, the correlation with tumor volume was not statistically significant. Schmalisch et al. [15] reported that the degree of upper expansion of the saddle of the pituitary tumor (>8 mm sagittal plane, >12 mm coronal plane) had a strong correlation with the visual field defect pattern and degree of decreased visual acuity. Eda et al. [16] contended that the correlation between tumor size and the degree of visual field defect exists only when the optic chiasm is in a normal anatomical position. Thus, the prognosis for visual field recovery is not only related to tumor volume, but also to the complex interaction of such factors as the anatomical position of the optic chiasm, the anatomical position of the tumor, and the degree of upper expansion of the saddle.

The strength of the current study is that the preoperative pattern of the visual field defect was more thoroughly analyzed. Although the degree of preoperative visual field defect influenced prognosis, the visual field defect pattern of the most affected eye was not statistically important. In addition, prognosis was good when the position of the visual field defect did not include the center or the visual field defect was confined to the unilateral eye. As previously noted, the degree of compression of the optic chiasm by the tumor was reflected in the result of the preoperative visual field examination. It seems that the weaker the compression, the smaller the degree of preoperative visual field defect, and when the compression is in the surface of the optic chiasm, the visual field defect does not include the central portion. Therefore, a smaller preoperative visual field defect without central field involvement, due to weaker and peripheral

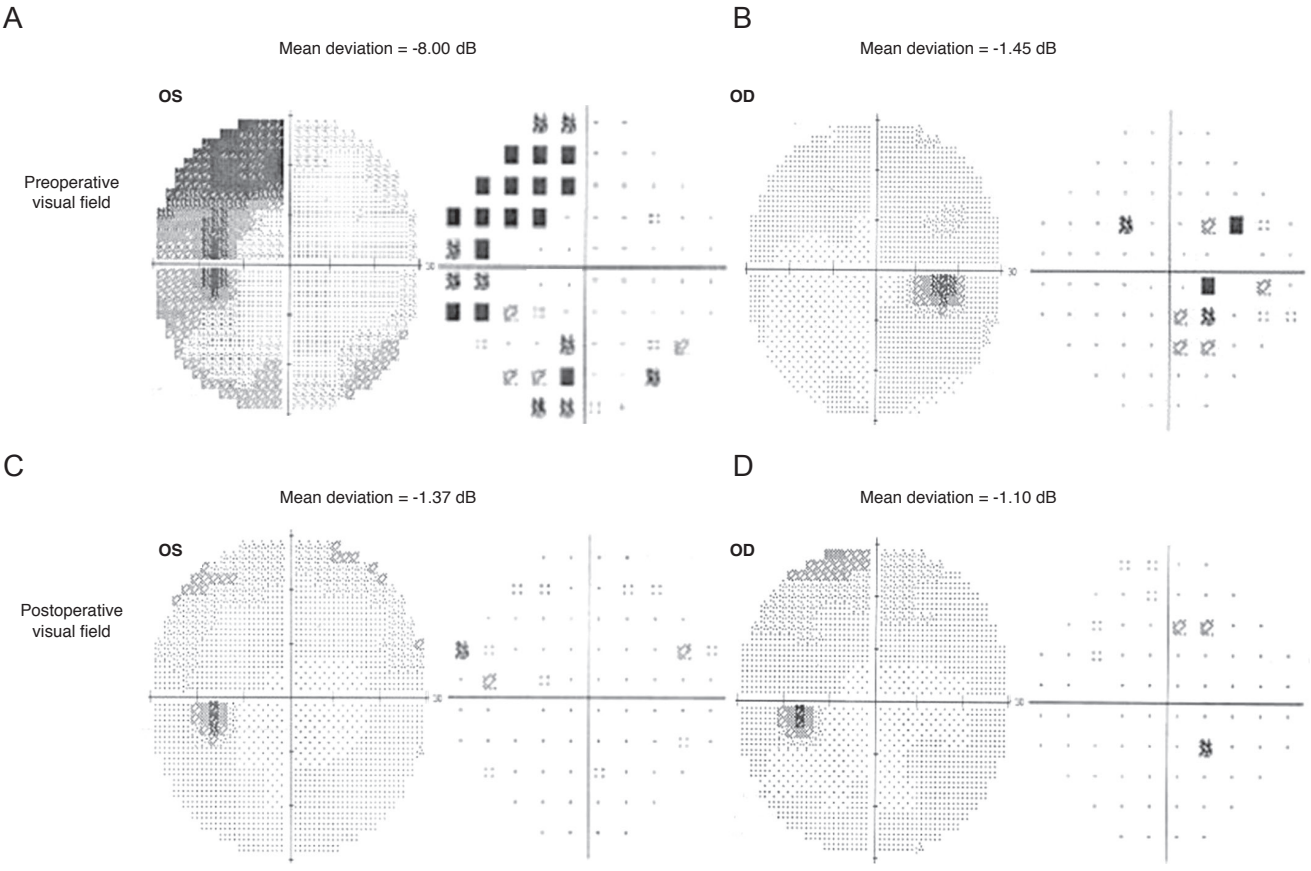

Fig. 2. A 42-year-old woman who was diagnosed with pituitary adenoma and underwent transsphenoidal surgery. (A) There was no central visual field defect in the preoperative visual field of the left eye (OS; mean deviation, -8.00 dB). (B) There is a normal visual field in the opposite eye (mean deviation, -1.45 dB). (C,D) There is marked visual field recovery in the postoperative visual field of the OS at 12 months after transsphenoidal surgery. OD = right eye.

compression of the optic chiasm, was associated with a higher possibility of postoperative visual field recovery.

A limitation of this study is that it focused on neurological symptoms and did not analyze any endocrine abnormalities that patients with a functional pituitary adenoma may have. Furthermore, in this study, the collection of the neurological symptom data and the period from symptom onset to surgery was based on patient self-reporting. As the data were based on patient self-reporting, the accuracy may be lower and recall bias by the patients may be present.

In conclusion, the factors related to postoperative visual field recovery in patients with pituitary adenoma with visual field defects include age, preoperative MD value, central visual field defect, and bilateral visual field defect. The postoperative visual field recovery is more promising when the patient is younger, the preoperative MD is better, the central visual field is not involved in the most affected eye, and the visual field defect is confined to the unilateral eye. Identifying such clinical factors might be useful for predicting the postoperative prognosis of patients with pituitary adenoma.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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