Predictive value of macular ganglion cell-inner plexiform layer thickness in visual field defect of pituitary adenoma patients: a case-control study

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Abstract

Objective

The present study explored the association between preoperative macular ganglion cell-inner plexiform layer thickness (GCIPL) and retinal nerve fiber layer thickness (RNFL) measured by optical coherence tomography (OCT) and the recovery of visual field (VF) defect after surgery in pituitary adenoma patients.

Methods

This case-control study included patients with pituitary adenoma in the Neurosurgery Department of Shanxi Provincial People's Hospital between October 2019 and June 2021. Cranial MRI examination, three-dimensional OCT, and VF testing (Humphrey Field Analyzer II750) were performed before and at 6months after the surgery.

Results

Fifty-three pituitary adenoma patients (81 eyes) were enrolled; 15 patients (23 eyes) were in the visual field did not recover group (VFNR), and 38 patients (58 eyes) were in the visual field recovered group (VFR). The temporal RNFL (P = 0.002) and average RNFL (P = 0.009) in the VFNR group were significantly lower than in the VFR group. The superior nasal GCIPL (P = 0.001), inferior nasal GCIPL (P = 0.001) and average GCIPL (P = 0.01) were significantly lower in the VFNR group than in the VFR group (all P < 0.01).The multivariable logistic regression analysis showed that nasal inferior GCIPL was an independent risk factor for VF recovery (odds ratio (OR) = 1.376,95% confidence interval (CI):1.089-1,739,P = 0.007). In the received operating characteristics (ROC) analysis, the area under the ROC curve (AUROCs) was the highest for nasal inferior GCIPL (AUROC = 0.739).

Conclusion

In patients who underwent resection of pituitary adenoma, nasal inferior GCIPL was an independent risk factor of visual field defect recover after surgery.

Introduction

Pituitary adenoma refers to a benign pituitary neoplasm that arises from adenohypophyseal cells [1–3]. The reported prevalence of pituitary adenoma is 7-41.3 per 100,000 individuals[1, 2]. Pituitary can induce endocrine abnormality, visual impairment, headache, and cognitive impairment; among these, visual impairment is the most common symptom and is reported by 32%-70% of the patients[1–3]. Visual impairment mainly includes visual acuity (VA) reduction and visual field (VF) defect, with VF defect occurring earlier than VA reduction. An impaired visual function has a long-term effect on the quality of

life and work of patients with pituitary adenoma and survivors[4, 5]. Therefore, the early detection of preoperative VF defects, postoperative VF recovery, and timely initiation of treatment or referral for visual rehabilitation is crucial to preserve visual function and improve quality of life [6, 7].

Optical coherence tomography (OCT) provides a reliable and objective tool for assessing and monitoring the state of the retina[8, 9]. OCT measures the peripapillary retinal nerve fiber layer thickness (pRNFL), macular ganglion cell complex thickness (mGCC), and macular ganglion cell-inner plexiform layer thickness (mGCIPL), which is a reliable indicators that directly reflect the severity of ganglion cell damage[8, 9]. In glaucoma, VF defects will appear when a significant proportion (30%-50%) of the ganglion cells are lost[10].

Visual impairment induced by pituitary adenoma, either compression or ischemia, damages the ganglion cells [11]. The literature suggests diagnostic and prognostic abilities of GCC and RNFL measurements to detect preoperative VF defects and postoperative VF recovery in pituitary adenoma patients [11–14]. High pRNFL, especially in the lower quadrants, is associated with high possibilities of postoperative VF recovery, irrespective of the severity of the preoperative VF defect [11–14]. In addition, the sensitivity and specificity of mGCIPL in detecting early lesions are higher than those of pRNFL and mGCC, and the reliability and robustness are higher in pituitary adenoma patients [15–17]. Nevertheless, little is known about the predictive value of mGCIPL in the recovery of visual functions in patients with pituitary adenoma. Therefore, this study aimed to explore the association between GCIPL and RNFL and VF defect recovery in patients with pituitary adenoma.

Methods

Study design and subjects

This case-control study included patients with pituitary adenoma in the Neurosurgery Department of Shanxi Provincial People's Hospital between October 2019 and June 2021. The inclusion criteria were 1) diagnosed with pituitary adenoma by cranial magnetic resonance imaging (MRI) on hospital admission, underwent transsphenoidal resection of pituitary adenoma, and confirmed as pituitary adenoma by postoperative pathological examination; 2) preoperative cranial MRI showed optic chiasm compression (or not), and cranial MRI in 3 months after the surgery did not show any optic chiasm compression; 3) corrected visual acuity (CVA) ≥0.1, and could cooperate with the VF test; 4) VF test showed typical temporal VF defect accompanied with (or not) nasal VF defect, and 5) age ≤ 70-years-old. The exclusion criteria were 1) patients with recurrent pituitary adenoma; 2) patients with anterior segmen,retinal or optic nerve disease ; 3) VF test results were unreliable (i.e., the rates of false positive, false negative, or fixation loss were >25%); 4) history of glaucoma and IOP >21 mmHg; 5) patients with diabetes, high myopia, or other systemic diseases or condition that influenced the retina or optical nerve; or 6) could not adhere to follow-up. This study followed the Declaration of Helsinki and was approved by the Ethics Committee of Shanxi Provincial People's Hospital.

Procedures

Cranial MRI examination was performed before and at 3 months after the surgery to clarify the correlation between pituitary adenoma and optic chiasma. Optic chiasma compression was defined as a visible contact of the highest point of pituitary adenoma to the optic chiasma on at least one image, with optic chiasma up-shifting. MRI images were evaluated tumor size,because the shape of pituitary tumor is irregular,and the vertical diameter has greatest influence on optical chiasma,the latter is used to defined the size of the tumor.Vertical diameter refers to the height from the bottom to the top of the tumor measured on the largest coronal plane of the tumor,the MRI images was performed by a radiologist who was blinded to the patients' data.The bilateral VA and CVA were assessed using a standard VA chart. The VF test was repeated after correction of refractive errors using the Central 24-2 SITA FAST software and a Humphrey Field Analyzer II750 (Carl Zeiss AG, USA). The reliability parameters, including false-positive rate, false-negative rate, and fixation loss rate, were maintained at <20%. The mean deviation (MD) of the VF indices was measured to reflect the degree of VF defect. The OCT examination was performed using three-dimensional (3D) OCT (3D OCT-2000 software version 8.00; Topcon, Tokyo, Japan) at a scanning rate of 50,000 A scans/s. The 3D disc 6×6 mode was used to measure the average and superior, inferior, nasal, and temporal RNFL by scanning the peri-optic disk. The macular mode included a 512 (vertical scan) × 128 (horizontal scan) matrix with the raster scanning of the central fovea s 7 mm^2 and the scanning of the central fovea with an area of 6×6 mm. The average value of a 10×10 square was automatically calculated by the software, and the quadrants that centered on the macular central fovea were divided into four sections: nasal superior, nasal inferior, temporal superior, and temporal inferior. All patients were examined by the same investigator. Only well-focused, well-centered images with high signal intensities (≥25) and no artifacts from eye movements were used for analysis. The distance between the external border of RNFL and IPL was defined as the mGCIPL.

The demographic characteristics of the patients, including sex and age,duration of symptom from the first visual symptoms to diagnosis of the tumor,tumor size,tumor type were collected. The optical examination parameters, such as VA, best CVA, IOP, diopter, ocular fundus, VF defect degree, RNFL, and GCIPL, were measured before and 6 months after the surgery. In addition, the data of the optic chiasma before and at 3 months after the surgery were recorded.

Temporal VF defect was defined as complete or partial temporal VF defect. No VF defect was defined as the absence of ≤3 continuous scotomas with the probability <5%, shown by pattern deviation probability plot (PDPP).The recovery of VF defect was defined as mean deviation (MD) ≥ -4dB and the absence of ≤3 continuous scotomas with the probability <5%, shown by pattern deviation probability plot (PDPP).The patients were divided into the VF did not recover group (VFNR), and the VF recovered group (VFR).

Statistical analysis

SPSS 22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. A normality test was performed for the continuous data. Normally distributed continuous data were presented as means ± standard deviations and compared using the t-test. Continuous data with a skewed distribution were

described as median (Q25, Q75) and compared using a non-parametric test. The categorical variables were described as n (%) and analyzed using the chi-square test or Fisher's exact test. The risk factors for VF defect improvement were assessed by multivariable logistic regression analysis. Receiver operating characteristics (ROC) curve analyses were performed. Two-sided P-values <0.05 indicated statistical significance.

Result

Characteristics of the patients

The baseline characteristics of the patients are shown in Table 1. The cohort comprised 53 patients (81 eyes), of which 21 (50.9%) and 32 (49.1%) were males and females, respectively. The patients were divided into the VFNR (15 patients, 23 eyes) and the VFR (38 patients, 58 eyes). The patients in the VFVR and VFR groups were 57 (50–63) and 54 (44–57) years old, respectively (P = 0.077). There were no differences between the two groups regarding IOP (P = 0.654), BCVA (P = 0.957), diopter (P = 0.822), and initial MD (P = 0.821), duration of symptom,tumor size and the pathological pattern of the tumor, but the final MD was higher in the VFR group compared with the VFNR group (median, -2.87 vs. -10.64 dB, P < 0.001).The pathological results of 15 patients inVFR group showed 10 gonadotropin adenoma,3 adrenocorticotrophic hormone adenoma and 2 prolactin adenoma.In VFNR group,there were 21patients for gonadotropin adenoma,4 patients for adrenocorticotrophic hormone adenom,7 patients for prolactin adenoma,3 patients for growth hormone adenom and 3 for mixed adenom, there were no differences between the two groups in pathological pattern of the pituitary adenoma.

Table 1
Demographic characteristic

Variables	VFNR (n = 15)	VFR (n = 38)	P
Number of affected eyes	23	58	
Sex,n(%)			0.972
Male	6 (40.0)	15 (39.5)	
Female	9 (60.0)	23 (60.5)	
Age (years)	57 (50, 63)	54 (44, 57)	0.077
Intraocular pressure (mmHg)	15.69 ± 2.63	15.39 ± 2.72	0.654
BCVA (logMAR)	0.9 (0.6, 1.0)	0.85 (0.6, 1.0)	0.957
Diopter (D)	0.0 (0.0, 0.2)	0.1 (0.0, 0.2)	0.855
Initial MD (dB)	-14.05 ± 4.08	-13.80 ± 4.67	0.821
Final MD (dB)	-10.64 (-14.37, -8.95)	-2.87 (-4.18, -2.02)	< 0.001
Duration of symptom(month)	6(2,15)	6(3,12)	0.939
Size of tumor(cm)	2.8(2.5,3.6)	2.7(2.36,3.34)	0.556

VFNR: visual field did not recover; VFR: visual field recovered; BCVA: best-corrected visual acuity; MD: mean deviation.

RNFL and GCIPL before the surgery

The preoperative temporal RNFL (52.2 ± 9.2 vs. 61.3 ± 12.7 μm, P = 0.002) and average RNFL (81.7 ± 8.0 vs. 87.5 ± 9.0 μm, P = 0.009) in the VFNR group were significantly smaller than in the VFR group. In addition, the superior nasal GCIPL (55.3 ± 7.0 vs. 62.0 ± 8.1 μm, P = 0.001), inferior nasal GCIPL (median, 53.1 vs. 57.4 μm, P = 0.001), and average GCIPL (59.6 ± 6.0 vs. 63.1 ± 5.2 μm, P = 0.01) were significantly lower in the VFNR group than in the VFR group (Table 2). There were no significant differences between the two groups regarding the other parameters (all P > 0.05).

Table 2
RNFL and GCIPL before the surgery

	VFNR group (n = 15)	VFR group (n = 38)	t/z	P
RNFL (μm)				
Superior	105.86 ± 10.66	109.18 ± 12.39	-1.128	0.263
Inferior	110.95 ± 8.94	115.50 ± 11.72	-1.673	0.098
Temporal	52.17 ± 9.22	61.29 ± 12.67	-3.131	0.002
Average	81.73 ± 7.96	87.51 ± 8.98	-2.691	0.009
Nasal, median (25th ,75th)	53 (45, 63)	62 (48.75, 74)	-1.472	0.141
GCIPL (μm)				
Temporal superior	64.58 ± 7.52	65.34 ± 5.23	-0.520	0.604
Nasal superior	55.32 ± 7.04	62.04 ± 8.14	-3.475	0.001
Average	59.60 ± 6.01	63.14 ± 5.17	-2.647	0.01
Temporal inferior	66.24 (63.64, 68.92)	66.28 (63.04, 70.75)	-0.367	0.714
Nasal inferior	53.08 (46.88, 57.52)	57.38 (54.06, 63.73)	-3.341	0.001

VFNR: visual field did not recover; VFR: visual field recovered; RNFL: retinal nerve fiber layer thickness; GCIPL: macular ganglion cell-inner plexiform layer thickness.

Data are presented as mean ± standard deviation, median (Q25, Q75), or n (%).

Multivariable analysis

The multivariable logistic regression analysis showed that the nasal inferior GCIPL was an independent risk factor for VF defect after surgery (odds ratio = 1.376, 95% confidence interval (CI): 1.089−1.739, P = 0.007) (Table 3). Nasal superior GCIPL, average GCIPL, temporal RNFL, and average RNFL were not independently associated with postoperative VF.

Table 3
Multivariable logistic regression

Variables	Multivariable analysis		
	OR	95% CI	P
Nasal superior GCIPL	1.122	0.856–1.471	0.404
Nasal inferior GCIPL	1.376	1.089–1.739	0.007
Average GCIPL	0.783	0.610–1.006	0.056
Temporal RNFL	1.051	0.993–1.113	0.085
Average RNFL	0.997	0.908–1.094	0.945

OR: odds ratio; CI: confidence interval; GCIPL: macular ganglion cell-inner plexiform layer thickness; RNFL: retinal nerve fiber layer thickness.

ROC analysis

the area under the ROC curve of nasal inferior GCIPL is 0.739, Cutoff value is 60.3μm

Variable	AUROC	P	95% CI		Cutoff value (μm)
			Lower limit	Upper limit	
Nasal inferior GCIPL	0.739 ± 0.059	0.001	0.624	0.854	60.30

Discussion

This study suggested that preoperative temporal RNFL and average RNFL in VFNR were significantly lower compared with VFR. In addition, the superior nasal GCIPL, inferior nasal GCIPL, and average GCIPL differed significantly between the two groups. The nasal inferior GCIPL was an independent risk factor of VF defect recovery after surgery for pituitary adenoma.

Visual defects are among the most common clinical manifestations of pituitary adenomas[1–3], because pituitary adenomas can compress the optic chiasma, leading to visual defects due to damaged ganglion cells [11]. Visual improvement after transsphenoidal surgery is a complex and lengthy process.The recovery of visual field is closely related to the number of ganglion cells in the visual pathway. Howerve,no examination has yet been made to distinguish reversible and irreversible ganglion cells and axons. Previous studies on the predictors of visual function recovery after pituitary tumor surgery have been done. The possible predictors are: duration of symptoms, paleness of optic disc, age, preoperative

mean deviation, size of tumor, and peripapillary retinal nerve fiber layer thickness[18, 19]. These factors were also considered in this study. However, symptom duration, age, preoperative MD value and tumor size have no statistically significant difference between the two groups in all preoperative comparisons.

OCT is an optimal examination to determine the state of the retina. Previous OCT studies revealed that pituitary adenoma could lead to ganglion cell loss[11–14]. Still, previous studies in glaucoma showed that the ganglion cell loss threshold to cause VF defect can be substantial (30%-50%), as reviewed by Hood et al[10]. The VF can recover after pituitary adenoma removal[6, 7], but whether this recovery could be suggested by preoperative OCT parameters was not described before. This study showed that the temporal RNFL and average RNFL in the VFNR group were significantly lower than in the VFR group and that the superior nasal GCIPL, inferior nasal GCIPL, and average GCIPL were significantly lower in the VFNR group than in the VFR group. Still, among those parameters, only nasal inferior GCIPL was an independent risk factor for VF defect recovery after surgery. Zhang et al. [20]showed that in patients with pituitary adenoma of temporal visual field defect, the GCIPL was thinner in the nasal quadrant in patients with VF defect than those without VF defect.

Previous studies suggested that preoperative RNFL is an indicator predicting the possibility of VF improvement after pituitary adenoma surgery [21–23]. Danesh-Meyer et al.[21] reported that VA and VF improved significantly at 6 weeks after surgery in patients with normal preoperative RNFL, while the VF improvement was not significant for patients with thin RNFL before surgery. Shin et al. [17]showed the RNFL in the inferior quadrants had the highest correlation with postoperative VF improvement. Moon et al. [24] suggested that the RNFL of all quadrants except for nasal RNFL was significantly correlated with postoperative VF improvement, and the correlation between temporal RNFL and postoperative VF improvement was the highest. In addition, the papillomacular bundle area was the most severely influenced area that could access the optic disc through temporal quadrants [24].The comparison of VF in pituitary adenoma patients in this study at 6–9 months showed that the temporal RNFL and average RNFL was thinner in the VFVR group than in the VFR group, but it was not supported by the multivariable logistic regression analysis.This could be due to the limited people in the group or ethnic differences.Nevertheless, the thinning of RNFL could reflect the degeneration of the optic nerve axon secondary to compression but not the loss of retinal ganglion cells.

In the present study, GCIPL was selectively measured during macular scanning to evaluate the loss of retinal ganglion cells and axon degeneration. The findings showed that the nasal superior and inferior GCIPL measured in preoperative macular scanning were significantly correlated with postoperative visual field recovery and were substantially thinner in the VFNR group than in the VFR group. The multivariable logistic regression analysis showed that both nasal superior and inferior GCIPL were significantly correlated with postoperative VF improvement, and the correlation was more prominent than RNFL. The ROC analysis suggested that nasal inferior GCIPL in the macular area could be a valuable predictive tool for VF recovery after pituitary surgery. Still, the AUROC was < 0.75, indicating that it cannot predict the outcomes in all patients. Future studies could examine combinations of factors that could improve this prediction.

The present study has several limitations. Firstly, the sample size of this study was not big, which might lower the methodological quality of the included studies. Secondly, only typical VF patients with bilateral temporal hemianopsia were included in this study. Unilateral temporal hemianopia patients should be included to broaden our findings in the future as it is a pilot study.

In summary, nasal GCIPL was an independent risk factor for VF recovery after pituitary adenoma surgery. Long-term, large-scale longitudinal studies are needed to obtain definitive data on RNFL and GCIPL changes in pituitary adenoma patients after surgery.

Declarations

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