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 (GCICPL) 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 GCICPL (P=0.001), inferior nasal GCICPL (P=0.001) and average GCICPL (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 GCICPL 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 GCICPL (AUROC =0.739).

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

Keywords  Pituitary adenoma · Optical coherence tomography · Visual field defect · Case-control

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 indicator that directly reflects 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 that 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 a high possibility 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; (2) patients with anterior segment, retinal or optic nerve disease; (3) 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. There was no cup disk ratio > 0.4, no optic disc pallor and no retinal hemorrhage. The exclusion criteria were (1) patients with recurrent pituitary adenoma; (2) patients with anterior segment, retinal or optic nerve disease; (3) VF test results were unreliable (i.e., the rates of false positive, false negative, or fixation loss were > 20%; 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

Craniath 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 define 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 mm² 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 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, according to the classification of H-P-A visual field defect, an early defect must be MD < -6 dB and the number of points with P < 5% is less than 18, and the number of points with P < 1% is less than 10 on the pattern deviation probability plot (PDPP). We defined the recovery of VF defect as MD ≤ -5 dB and the absence of ≤ 3 contiguous scotomas with the probability < 5% or 1% on the pattern deviation probability plot. 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. Spearman’s rank correlation was used to examine relationships between structural and functional data.

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 VFR and VFVR 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 = 0.009). 17 of 58 eyes had MD values less than –3 dB and 41 eyes had MD values greater than –3 dB in the VFR group. The pathological results of 15 patients in VFR group showed 10 gonadotropin adenoma, 3 adrenocorticotropic hormone adenoma, and 2 prolactin adenoma. In VFNR group, there were 21 patients for gonadotropin adenoma, 4 patients for adrenocorticotropic hormone adenoma, 7 patients for prolactin adenoma, 3 patients for growth hormone adenoma and 3 for mixed adenoma, there were no differences between the two groups in pathological pattern of the pituitary adenoma.

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 statistically different between the two groups.
ROC analysis

The area under the ROC curve of nasal inferior GCIPL is 0.739, Cutoff value is 60.3 μm (Table 4).

Inferior RNFL thickness Temporal RNFL thickness 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]. Because pituitary tumor and optic chiasma position difference and varying degrees of compression of the optic chiasm by the tumor, It can cause various types of visual field defect, such as central dark spot, partial central dark spot, homonymous hemianopia However, the most typical and common type

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 2  RNFL and GCIPL before the surgery

| Variable          | 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     |                     |                    |     |     |
| Superior          | 53 (45, 63)         | 62 (48.75, 74)     | -1.472 | 0.141 |
| Inferior          |                     |                    |     |     |

Table 3  Multivariable logistic regression

| Variables         | Multivariable analysis |
|-------------------|------------------------|
| Nasal superior GCIPL | 1.122          |
| Nasal inferior GCIPL | 1.376          |
| Average GCIPL      | 0.783          |
| Temporal RNFL      | 1.051          |
| Average RNFL       | 0.997          |

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

The asterisk indicates statistical signifiance, P < 0.05

Table 4  the area under the ROC curve of nasal inferior GCIPL

| Variable         | AUROC         | 95% CI       | Cutoff value (µm) |
|------------------|---------------|--------------|-------------------|
| Nasal inferior GCIPL | 0.739 ± 0.059 | 0.624 – 0.854 | 60.30             |

Table 5  Relationship between GCC parameters, RNFL thickness parameters and MD

| MD   | P value |
|------|---------|
| RNFL thickness |     |
| Superior | 0.097 | 0.387 |
| Inferior | 0.244* | 0.028 |
| Temporal | 0.243* | 0.029 |
| Nasal | 0.189 | 0.091 |
| Average | 0.253* | 0.023 |
| GCIPL thickness |     |
| Temporal superior | 0.133 | 0.238 |
| Temporal inferior | 0.140 | 0.212 |
| Nasal superior | 0.150 | 0.182 |
| Nasal inferior | 0.233* | 0.036 |
| Average | 0.200 | 0.074 |

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.
of visual field defect is bilateral temporal hemianopia. Further development will lead to subnasal visual field defect and total blindness. In our research, 8 cases of 81 eyes were associated with subnasal visual field defect. 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. However, 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 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.

In this study, we examined the relationship between structural and functional measures of optic nerve dysfunction in patients with pituitary tumor with temporal VF defect. The results show a moderate correlation between structure and function. temporal VF defect is associated with thinning of temporal RNFL thickness and nasal GCIPL thickness, which is consistent with other findings [13, 20, 25]. The correlation coefficient is low because the visual field reflects the whole visual path, while GCIPL and RNFL reflect the number of optic ganglion cells and the integrity of axons in the central region, and the patients are limited to pituitary tumor patients with temporal VF defect, not including normal visual field or other types of visual field defects.

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 hemianopia 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.
Author contributions LX, XYP and WHJ performed the initial experimental design, WFX, ZW and YJH helped to collect the cases and completed relevant inspection, LX produced the first draft of the manuscript and figures. X.WY reviewed statistical analysis, XYP and WHJ edited the manuscript, contributing to the final version sent for approval. All authors read and approved the final manuscript.

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Declarations

Conflict of interest The authors have no potential conflicts of interest to disclose. The participants were informed of the study objectives and signed the informed consent form.

Research involving human participants, their data or biological material This study was approved by the Ethics Committee of Shanxi Provincial People’s Hospital and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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