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Opinion paper

Ganglion cell complex loss precedes retinal nerve fiber layer thinning in patients with pituitary adenoma

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ABSTRACT

1. Background

Pituitary adenomas are one of the most common types of brain tumors, accounting for 15% of all intracranial neoplasms [1]. Visual disturbances are noted when the tumor grows beyond the sella and compresses the optic nerve. Typical neuro-ophthalmic features include progressive bilateral slow and asymmetric deterioration in visual field defects and optic disc changes.

Retinal ganglion cell elements exist in 3 layers in the retina: the retinal nerve fiber layer (ganglion cell axons), the ganglion cell layer (ganglion cell bodies), and the inner plexiform layer (ganglion cell dendrites). The new generation of spectral-domain OCT (SD-OCT) instruments enables clinicians to measure the combined thickness of the nerve fiber layer, the ganglion cell layer, and the inner plexiform layer, collectively known as the ganglion cell complex (GCC) [2]. Previous studies of patients with large pituitary tumors that induce optic chiasm compression identified a diffuse loss of retinal nerve fiber layer (RNFL) and hypothesized that pituitary tumors may cause reversible RGC dysfunction [3,4].

All parameters related to GCC measurements are color coded to indicate significant GCC thickness reductions. But so far, little attention has been paid to the size damaged areas of the GCC marked by either red or yellow on the significance map. In addition, the pattern of retinal ganglion thickness changes over time is not clear. The purpose of our study was to investigate the changes observed in the perimetry, RNFL and GCC over time in patients with pituitary adenomas.

2. Methods

The procedures followed the tenets of the Declaration of Helsinki, and written informed consent was obtained from all participants. Patients with pituitary adenomas were recruited from Huashan Hospital between September 2012 and September 2015. Pituitary adenoma was confirmed by pathology. Patients underwent a thorough ophthalmic examination by experienced ophthalmologists, which included pupil and anterior and posterior segment examination. Patients with other ocular diseases were excluded.

Static automated perimetry (SAP) was performed using the Humphrey 750 Visual Field Analyzer (Zeiss-Humphrey Systems, Dublin, CA, USA) and a central 30-2 threshold protocol. Fixation loss was less than 20%. The false positive error rate was less than 20% and the false negative error rate was less than 20%. Mean deviation (MD) was automated given by the machine.

RTVue (Optovue, Fremont, CA, USA) using a three-dimensional disc and optic nerve head protocols was applied. The GCC thickness was measured from the internal limiting membrane to the inner plexiform layer. The RNFL 3.45 mode of the RTVue SD system measures the peripapillary RNFL thickness along the circumference of a

Abbreviations: MD, mean deviation in static automated perimetry; SAP, static automated perimetry; RNFL, retinal nerve fiber layer; GCC, ganglion cell complex.

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3.45-mm-diameter circle around the optic disc. The results were color-coded to indicate whether or not there was a significant reduction in GCC or RNFL thickness: P < 1% was color-coded red, P < 5% yellow, and P ≥ 5% green.

Abnormal areas of the RNFL or GCC on SD-OCT images (red areas) were analyzed with image J version 1.37v (National Institutes of Health, Bethesda, MD, USA) software. Percentage of abnormal area on RNFL or GCC map was expressed in %.

Patients were divided into three groups according to tumor heights on magnetic resonance imaging. MRI was performed to measure tumor height using a 3.0 T system (Siemens MAGNETOM Verio 3.0 T, German). Thin slice T1-weighted (repetition time/echo time 600/20 ms) imaging was performed in the sagittal plane followed by the coronal plane. Coronal and sagittal images were 1.5-mm thick with a 0-mm space between slices. The field of view was 20 cm, and the matrix size was 256 × 256. Tumor height was measured on the coronal image. A horizontal line was drawn at the level of the upper surface of the horizontal segment of the internal carotid artery within the cavernous sinus. The maximum suprasellar height of the adenoma perpendicular to that line was measured as tumor height.

Statistical analysis was performed using SPSS 11.0 for Windows (SPSS Inc, Chicago, IL, USA). The ANNOVA test was used to compare means.

3. Results

3.1. General characteristics of patients assessed

Seventy-one patients (142 eyes) with pituitary adenomas, fifty males and twenty-one females, with an average age of 36 were assessed. 56 patients were with visual field defect. The other 15 patients were without visual field defect but with confirmed optic chiasm compression on MRI. The SAP before surgery was 10.6 db for the left eye and 10.8 db for the right eye, percentage of abnormal RNFL was 9% for the left eye and 7% for the right eye. Percentage of abnormal GCC was 29% for the left eye and 30% for the right eye.

3.2. SAP, RNFL and GCC in patients with different tumor heights

Patients were divided into three groups according to tumor heights: small (less than 1.5 cm), medium (1.5 cm or more than 1.5 cm and less than 2.5 cm) and large (2.5 cm or more than 2.5 cm). SAP, RNFL and GCC were compared between groups (Table 1). SAP and RNFL were basically normal (SAP-L: −4.3 db, SAP-R: −4.8 db, RNFL-L: 1%, RNFL-R: 1%) in patients with small tumors with little decrease of GCC (GCC-L: 9%, GCC-R: 13%). SAP decreased (SAP-L: −11.9 db, SAP-R: −11.5 db) and percentage of abnormal GCC increased (GCC-L: 37%, GCC-R: 36%) in medium tumors, while RNFL remained normal (RNFL-L: 7%, RNFL-R: 5%). In large tumors, further decrease of SAP (SAP-L: −17.4 db, SAP-R: −16.8 db) and increase of abnormal RNFL and GCC (RNFL-L: 31%, RNFL-R: 24%, GCC-L: 52%, GCC-R: 53%) was observed.

ANNOVA test with LSD test to compare averages between different groups were also carried out. The result was shown in Table 2. Worse visual field was demonstrated comparing patients with medium tumors and small tumors, and the worst in patients with large tumors (Fig. 1). GCC also follows this pattern: the best in small tumors, worse in medium tumors and the worst in large tumors. But for RNFL, although the percentage of abnormal RNFL increased in patients with medium tumors, the result does not reach statistical significance. RNFL increased obviously for larger tumors.

4. Discussion

We brought out the size of damaged areas of the GCC marked by either red or yellow on the significance map in patients with pituitary adenomas. In addition, a new pattern of retinal ganglion thickness changes over time in patients with pituitary adenoma was also shown in this study. When the optic chiasm was touched by the tumor but not compressed, GCC thickness decreased first, without RNFL thinning or visual field defect. As the tumor enlarged, GCC thickness decreased further with visual field defect, still without RNFL thinning. When the tumor grows further larger with severe optic chiasm distortion, RNFL started to decrease with further GCC thinning and visual field defect (Fig. 2).

Previous studies have evaluated RNFL and GCC thickness in patients with pituitary adenomas, specifically in those with chiasma compression [5,6]. Stratus OCT revealed a diffuse loss of RNFL particularly in the nasal and temporal aspects of the optic nerve in patients with long-standing bitemporal visual field defects. But no previous study show any chronological change regarding RNFL and GCC. In our study, we found GCC thinning in patients with pituitary adenoma of normal visual field without chiasma compression. Ventura et al. reported that pituitary tumors, even in the absence of a compressive effect at the chiasm on MRI [7], may cause reversible RGC dysfunction, which precedes visual field loss and RGC death. Cennamo et al. also found that pituitary macro-adenomas, even in the absence of chiasma compression, may induce GCC thinning [8]. The presence of a pituitary tumor, even in the absence of compressive effect at the chiasm on MRI, may cause GCC thinning, which precedes visual field loss.

Traditionally, when a pituitary adenoma begins compressing the axons of the anterior visual pathway, an immediate physiological conduction block ensues, consequently leading to loss of visual field. The slow, chronic nature of adenoma results in axoplasmic stasis before RGCs and nerve fibers are permanently damaged by progressive axonal injury. Before the operation, there is a difference in the timing of changes in the visual field and changes in RNFL because damage to RNFL does not occur via a direct process

Table 1
Comparison among patients with different tumor heights.

Tumor		Small (<1.5)	Medium (1.5–2.5)	Large (≥2.5)
Female		8/21	9/38	4/12
Height		1.21 ± 0.04	1.94 ± 0.05	2.93 ± 0.19
SAP (db)	L	−4.3 ± 0.7	−11.9 ± 1.1	−17.4 ± 2.7
	R	−4.8 ± 1.0	−11.5 ± 1.2	−16.8 ± 2.6
GCC	L	9% ± 3%	37% ± 6%	52% ± 12%
	R	12% ± 3%	36% ± 5%	53% ± 10%
RNFL	L	1% ± 1%	7% ± 3%	31% ± 11%
	R	1% ± 1%	5% ± 3%	24% ± 10%

SAP: static automated perimetry.
GCC: ganglion cell complex.
RNFL: retinal nerve fiber layer.