CLINICAL RESEARCH

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Accept	ed: 2015.10.10 ed: 2015.12.03 ed: 2016.07.03	-	Evaluation of Macular G and Peripapillary Retina Primary Craniopharyngi Optical Coherence Tomo	l Nerve Fib oma by Fou	er Layer in			
I Stat Data Manuscr Lit	ors' Contribution: Study Design A Data Collection B istical Analysis C Interpretation D ipt Preparation E terature Search F ands Collection G	BCD EF	Liu Yang Yuanzhen Qu Wen Lu Fengjun Liu	Department of Ophthalmology, University, Beijing, P.R. China	Beijing Tian Tan Hospital, Capital Medical			
Corresponding Author: Source of support:		-	Liu Yang, e-mail: yangliu893209@163.com This work was supported by the High-Level Technical Training Project Funding of the Beijing Health System (No. 2013-3-051)					
Background: Material/Methods:			The aim of this study was to compare the differences in macular ganglion cell complex (GCC) and peripapil- lary retinal nerve fiber layer (pRNFL) in child and adult patients with primary craniopharyngioma by Fourier- domain optical coherence tomography (FD-OCT) and to evaluate their significance in the diagnosis of primary craniopharyngioma. Ninety-six participants were divided into 3 groups: 32 in the child craniopharyngioma group (CCG) and 32 in the adult craniopharyngioma group (ACG) who were treated in Beijing Tiantan Hospital between November 2013 and October 2014, and 32 in the normal group (NG). All subjects were scanned by FD-OCT to map GCC and pRNFL thicknesse. Spearman correlation coefficient was used to assess the correlation between GCC and pRNFL thickness, and pRNFL thickness and optic nerve head (ONH) parameters, including horizontal cup-disc					
		Results: lusions:	ratio (HCDR), vertical cup-disc ratio (VCDR), optic disc The correlation between GCC and pRNFL thickness in significant difference in GCC thickness was observed ness in both the CCG and ACG was significantly higher ness was detected between the 2 craniopharyngioma nesses were negatively correlated with VCDR in the C GCC was more sensitive than pRNFL in detecting opti tients. A thinner pRNFL was especially correlated with	the CCG was slightly stro among the CCG, ACG, and than that in NG, no signif groups. The average, sup CG (in double eyes) and a tic nerve damage in the o	nger compared with the ACG. A NG. Although the pRNFL thick- icant difference in pRNFL thick- perior, and inferior pRNFL thick- ACG (only in left eyes). eyes of craniopharyngioma pa-			
	MeSH Key	ywords:	Craniopharyngioma • Optic Disk • Retinal Ganglio	n Cells				
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Background

Craniopharyngioma is the most common non-neural brain tumor derived from pituitary gland embryonic tissue; it occurs primarily in children but also in adults, with an incidence of approximately 2/100 000 [1,2]. Due to its sensitive sellar/suprasellar location and ability to form large cysts, ACP often exhibits locally aggressive behavior and damages vital structures of the pituitary, hypothalamus, and visual apparatus. Although considered benign, craniopharyngiomas may cause severe damage to the optic nerve with corresponding visual field loss or even blindness; therefore, early diagnosis and treatment are crucial for maintaining visual function and preventing vision problems.

The macular ganglion cell complex (GCC) is composed of the nerve fiber layer (NFL), the ganglion cell layer, and the inner plexiform layer [3]. Given the importance of the macula in visual function, several recent studies have focused on the association between changes in GCC thickness and visual loss and the diagnostic value of macular GCC parameters in glaucoma [3-7]. Retinal nerve fiber layer (RNFL) thinning can reflect axonal degeneration of optic nerve fibers secondary to optical chiasmal compression [8], but may not directly show the loss of retinal ganglion cell complex (GCC). Because structural damage may be detectable prior to visual loss on standard automated perimetry [9], several technologies have been used to provide objective and quantitative measurements of the retina to improve the diagnostic accuracy and reproducibility, including optical coherence tomography (OCT), scanning laser topography, and scanning laser polarimetry.

Optical coherence tomography (OCT) is a noninvasive method that is used to scan cross-sectional imaging of the retina. Traditional OCT can perform accurate and objective measurements of the retinal nerve fiber layer (RNFL) and optic nerve head (ONH) topography [10]. The recently developed FD-OCT instrument allows much higher axial resolution and scan speed (26 000 A-scans/second) compared with conventional timedomain OCT (TD-OCT, 400A-scans/second), and thereby provides better measuring segmentation of the macular region. We have previously shown that GCC and pRNFL thickness measured by RTVue OCT (Optovue, Inc., Fremont, CA, USA) is correlated with vision field defects, which can be used to quantitatively evaluate optic nerve damage in patients with saddle area tumors [11,12].

In this study, we assessed the GCC and pRNFL thickness measured by FD-OCT and compared their sensitivity for reflecting optic nerve damage in child and adult patients with primary craniopharyngioma. The ONH parameters were also determined by FD-OCT and the correlation between pRNFL thickness and these parameters was analyzed. Finally, we discuss the clinical significance of GCC and pRNFL thickness obtained by FD-OCT in the early diagnosis of primary craniopharyngioma.

Material and Methods

Subjects

Patients with primary craniopharyngioma confirmed by magnetic resonance imaging (MRI) and postoperative histological findings in Beijing Tiantan Hospital in China between January 2013 and October 2014 were consecutively selected for this study. Prior to surgery, all patients underwent a complete ophthalmological examinations including best-corrected visual acuity (BCVA), intraocular pressure measurements (IOP, Goldmann applanation tonometry), slit lamp biomicroscopy, funduscopy and stereoscopic optic nerve photography, and RTVue-100 OCT scanning (Optovue Inc., Fremont, CA, USA). Exclusion criteria were: any ocular diseases (including glaucoma and moderate or advanced cataract), previous ocular surgery or trauma, myopia greater than -6.00 diopters, history of using oral or topical steroids, and diabetes or any other systemic illness that may affect the retina and optic nerve. A total of 32 healthy controls without any ophthalmological disease were selected from the hospital staff. All participants signed the written informed consent form. The study protocol was approved by the Medical Ethics Committee of Beijing Tiantan Hospital according to the Declaration of Helsinki.

Fourier-domain optical coherence tomography (FD-OCT)

OCT imaging was conducted after pupil dilation using the RTVue-100 FD-OCT system (Optovue, Inc., Fremont, CA, USA) using GCC and ONH scan patterns. The GCC scan protocol consisted of 14 928 A-scans over a 7-mm square area on the central macula in 0.6 seconds by using 1 horizontal line and 15 vertical lines at 0.5-mm intervals. The scan time was set to 0.6 seconds to reduce the problems of eye movement and corneal drying due to long scan time. The scans were centered 0.75 mm temporal to the fovea to improve the coverage of the temporal macula. Each eye was scanned 3 times. The GCC thickness was defined as the distance between the internal limiting membrane and the outer edge of the inner plexiform layer. The ONH scan used a combination of radial and circular scans centered on the ONH. The pRNFL scan protocol consisted of a 3.45-mm circle around the ONH to measure the thickness of the NFL. The following parameters were analyzed during the OCT ONH scanning: horizontal cup/disc diameter ratio (HCDR), vertical cup/disc diameter ratio (VCDR), optic disk area (ODA), and cup area (CA).

Statistical analysis

All data are presented as mean \pm standard deviation. Statistical analyses were performed using SPSS version 19.0 (SPSS Inc.,

Variables	CCG (n=32)	ACG (n=32)	NG (n=32)	P1	P2	P3
Mean age (years)	9.72±3.53	39.44±11.40	38.84±12.64			
Sex (male/female)	17/15	17/15	18/14			
GCC thickness, µm (OD/OS)						
Average	77.34±12.96/	89.78±9.54/	97.46±4.70/	0.000/	0.000/	0.000/
	78.07±12.31	88.45±10.67	97.67±3.59	0.003	0.000	0.000
Superior	77.36±13.23/	89.21±9.67/	97.14±4.70/	0.000/	0.000/	0.000/
	78.42±13.17	88.13±11.45	97.88±3.67	0.010	0.000	0.000
Inferior	77.34±13.06/	90.34±9.72/	97.79±5.11/	0.000/	0.000/	0.000/
	77.84±12.48	88.72±10.42	97.46±4.13	0.002	0.000	0.000
pRNFL thickness, µm (OD/OS)						
Average	92.38±23.06/	101.57±20.36/	115.62±9.25/	0.112/	0.000/	0.001/
	89.50±26.84	103.67±21.57	115.80±8.71	0.088	0.000	0.003
Superior	92.29±22.91/	101.40±21.39/	115.96±10.71/	0.133/	0.000/	0.001/
	94.90±30.50	105.54±24.45	119.69±8.73	0.129	0.000	0.004
Inferior	92.48±25.40/	101.74±20.70/	115.27±12.24/	0.123/	0.000/	0.002/
	89.96±29.57	101.81±21.50	113.16±10.51	0.083	0.000	0.007

Table 1. Baseline characteristics, and GCC and pRNFL thickness.

Data were shown as mean \pm standard deviation. *P1* – child patients *vs.* adult patients; *P2* – child patients *vs.* normal controls; *P3* – adult patients *vs.* normal controls; GCC – ganglion cell complex; pRNFL – peripapillary retinal fiber layer; CCG – child craniopharyngioma patient group; ACG – adult craniopharyngioma patient group; NG – normal group.

Chicago, IL, USA). The differences in the mean values among the CCG, ACG, and healthy subjects were obtained by pairwise comparison using *t* tests. The relationship between GCC and pRNFL thickness, pRNFL thickness, and each ONH parameter was assessed by Spearman ranked correlation analyses. P values of less than 0.05 were considered statistically significant.

Results

General characteristics

A total of 96 participants (192 eyes) including 32 subjects in the CCG (mean age 9.72 ± 3.53 years), 32 in the ACG (mean age 39.44 ± 11.40 years), and 32 in NG (mean age 38.84 ± 12.64 years) were analyzed in this study. There was no significant difference in mean age between the ACG and NG, or in sex distribution among the 3 groups. The general characteristics of subjects are shown in Table 1.

Comparison of GCC and pRNFL thickness in different groups

As shown in Table 1, the average, superior, and inferior GCC and pRNFL thickness in the CCG and ACG were significantly reduced compared with the normal controls. The GCC thickness in the CCG in the superior and inferior quadrants and the average value were significantly thinner compared with the ACG, whereas the average, superior, and inferior pRNFL thickness in the CCG was similar to that of the ACG.

Correlation between GCC and pRNFL thickness

The association between the average, superior, and inferior GCC thickness and corresponding pRNFL thickness was evaluated by Spearman correlation analyses (Table 2). Although the average, superior, and inferior GCC thickness was associated with corresponding pRNFL thickness in the CCG and ACG, the correlation in the CCG was stronger than that in the ACG (CCG: R=0.595~0.742, ACG: R=0.449~0.679).

Parameters of optic nerve head

As shown in Table 3, the values of HCDR, VCDR, ODA, and CA in the CCG were significantly higher compared with the NG. VCDR and CA values in the CCG were significantly higher than those in the ACG (p<0.05), whereas there was no significant difference in HCDR and ODA values between the 2 groups. In addition, the values of HCDR, VCDR, ODA, and CA in the ACG were similar to those in the NG.

The correlation between pRNFL thickness and each ONH parameter was analyzed by Spearman correlation analyses. As shown in Tables 4 and 5, in children with craniopharyngiomas,

Variables	Right	t eye	Left	eye
Variables	Р	R	Р	R
Adult				
Average thickness	0.007	0.467**	0.000	0.589**
Superior thickness	0.010	0.449*	0.005	0.488**
Inferior thickness	0.001	0.539**	0.000	0.679**
Child				
Average thickness	0.000	0.719**	0.000	0.672**
Superior thickness	0.000	0.742**	0.000	0.602**
Inferior thickness	0.000	0.656**	0.000	0.595**

Table 2. Spearman's correlation between GCC and pRNFL measurements.

* p<0.05; ** p<0.01.

Table 3. Characteristics of optic nerve head in children and adults with craniopharyngioma.

Variables (OD/OS)	Child patients (n=32)	Adult patients (n=32)	Normal control (n=32)	P1	P2	P3
HCDR	0.66±0.18/	0.61±0.18/	0.57±0.15/	0.260/	0.032/	0.317/
	0.69±0.18	0.62±0.20	0.57±0.17	0.126	0.007	0.249
VCDR	0.60±0.20/	0.50±0.19/	0.43±0.12/	0.047/	0.000/	0.050/
	0.62±0.21	0.51±0.14	0.48±0.15	0.023	0.005	0.370
ODA (mm²)	2.63±0.41/	2.47±0.50/	2.35±0.44/	0.100/	0.003/	0.247/
	2.53±0.43	2.44±0.48	2.41±0.41	0.358	0.047	0.791
CA (mm²)	0.92±0.57/	0.66±0.43/	0.51±0.31/	0.021/	0.001/	0.076/
	0.97±0.60	0.67±0.47	0.60±0.38	0.036	0.003	0.484

HCDR – horizontal cup/disc diameter ratio; VCDR – wertical cup/disc diameter ratio; ODA – optic disk area; CA – cup area; P1 – child patients vs. adult patients; P2 – child patients vs. normal controls; P3 – adult patients vs. normal controls.

a negative correlation was observed between: 1) the horizontal C/D ratio and the pRNFL thickness of the average, superior, and inferior quadrants in left eyes (p=.000); 2) the vertical C/D ratio and the pRNFL thickness of the average, superior, and inferior quadrants in double eyes (right eyes: p<0.05, left eyes: p<0.01); and 3) cup area and the pRNFL thickness of the average, superior, and inferior quadrants in the left eyes (p<0.01). In adult craniopharyngiomas, no correlation between pRNFL thickness and either HCDR or CA was detected in any quadrant. In addition, the average, superior, and inferior pRNFL thickness was negatively correlated with VCDR (in left eyes), but was positively correlated with ODA (in right eyes).

Discussion

Compression of the optic chiasm due to sellar tumors can lead to compromised visual function. Craniopharyngioma is a type of sellar tumor that may compress the optic chiasm and damage the optic nerve and visual function. It accounts for 1% to 4% of all primary intracranial tumors, and 5% to 10% of those are found in children [13].

Previous studies have shown that RNFL thinning reflects axonal degeneration of optic nerve fibers secondary to optic chiasmal compression [8]. The degree of RNFL thinning due to compression of sellar tumors has been found to be correlated with visual field defects [8,11,12]. OCT is a useful tool for objective and quantitative assessment of the structural and functional damage of RNFL and GCC in eyes with optic nerve impairments caused by chiasmal compression. RNFL and GCC thickness measured by OCT has been identified as useful prognostic indicators in the preoperative assessment of chiasmal compression [14]. Studies have confirmed the diagnostic performance of GCC thickness measured by OCT in the diagnosis and assessment of glaucoma [3,15,16]. In the present study, GCC and pRNFL thickness in both child and adult patients with primary craniopharyngioma was determined by the high-speed high-accuracy FD-OCT. A significant difference in GCC thickness was observed among the 3 groups (CCG, ACG,

able 4. Correlation between pRNFL thickness and ONH parameters in child craniopharyngioma.
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pRNFL thickness (OD/OS)	HCDR	VCDR	ODA (mm²)	CA (mm²)
Average thickness	R=-0.323/R=-0.605**	R=-0.370*/R=-0.703**	R=0.182/R=0.198	R=-0.255/R=-0.583**
Average thickness	P=0.071/P=0.000	P=0.039/P=0.000	P=0.318/P=0.277	P=0.159/P=0.000
Cuparias thiskness	R=-0.328/R=-0.593**	R=-0.379*/R=-0.648**	R=0.183/R=0.190	R=-0.255/R=-0.565**
Superior thickness	P=0.067/P=0.000	P=0.032/P=0.000	P=0.317/P=0.299	P=0.159/P=0.001
Inferior thickness	R=-0.329/R=-0.600**	R=-0.372*/R=-0.681**	R=0.151/R=0.229	R=-0.281/R=-0.556**
	P=0.066/P=0.000	P=0.036/P=0.000	P=0.411/P=0.207	P=0.120/P=0.001

* *p*<0.05; ** *p*<0.01. HCDR – horizontal cup/disc diameter ratio; VCDR – vertical cup/disc diameter ratio; ODA – optic disk area; CA – cup area.

Table 5. Correlation between pRNFL thickness and ONH parameters in adult craniopharyngioma.

pRNFL thickness (OD/OS)	HCDR	VCDR	ODA (mm²)	CA (mm²)
Average thickness	R=-0.106/R=-0.336	R=-0.167/R=-0.403*	R=0.413*/R=0.193	R=-0.125/R=-0.309
Average thickness	P=0.563/P=0.060	P=0.362/P=0.022	P=0.019/P=0.290	P=0.497/P=0.086
Currenter thiskness	R=-0.089/R=-0.274	R=-0.179/R=-0.463**	R=0.369*/R=0.177	R=-0.134/R=-0.319
Superior thickness	P=0.629/P=0.128	P=0.327/P=0.008	P=0.038/P=0.333	P=0.464/P=0.076
Inferior thickness	R=-0.139/R=-0.332	R=-0.118/R=-0.216*	R=0.402*/R=0.136	R=-0.073/R=-0.187
	P=0.449/P=0.063	P=0.520/P=0.048	P=0.023/P=0.459	P=0.691/P=0.306

* p<0.05; ** p<0.01; HCDR – the horizontal cup/disc diameter ratio; VCDR – vertical cup/disc diameter ratio; ODA – optic disk area; CA – cup area

and NG), whereas there was no significant difference in pRN-FL thickness between the CCG and ACG. Moreover, the correlation between GCC thickness and pRNFL thickness in the CCG was stronger compared with the ACG (CCG: R=0.595~0.742 vs. ACG: R=0.449~0.679). These results suggest that GCC was more sensitive than pRNFL in detecting optic nerve damage in the eyes of craniopharyngioma patients, and was especially useful in the diagnosis of childhood craniopharyngioma. Similar findings have been previously reported when the sensitivity of GCC and pRNFL in the diagnosis of pituitary tumor was compared [12]. Moreover, it has been shown that there was a highly significant negative correlation between average RNFL measurement and increasing age (3.3 microns per decade, <0.001). A significant negative correlation was also observed between increasing age and the RNFL measurements in all regions (<0.05) and decreasing age to a similar extent [17], indicating that the RNFL thickness might not be an accurate diagnostic indicator for craniopharyngioma.

Glaucomatous optic neuropathy and nonglaucomatous optic nerve damage cause a decrease in retinal arteriole diameter and a loss of RNFL [18]. In this study we showed that ONH parameters (including HCDR, VCDR, ODA, and CA) in children with craniopharyngioma were significantly higher than in adult patients and normal controls, but the average, superior, and inferior pRNFL thickness in child patients was much thinner than in the other 2 groups. We have previously demonstrated that glaucoma-like optic discs were detected significantly more frequently in patients with intrasellar or perisellar tumors compared with an age-matched population-based control group. Disc glaucoma has also been found in patients with meningiomas, pituitary gland adenomas, and craniopharyngiomas [17]. In the present study, glaucoma-like optic discs were detected in both eyes of these patients, despite normal intraocular pressure. The VCDR in the child patients was significantly higher compared with the control group, whereas the VCDR value in the adult patients was similar to that in the control group. The decreased structural integrity of optic nerve head in children with craniopharyngiomas might be associated with a retrograde degeneration from the chiasm to the optic disc. It remains unclear whether the degeneration can lower the threshold for intraocular pressure, leading to further glaucoma-like

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damage, in addition to the injuries caused by direct compression of the optic nerve fibers by the tumor. Some clinical studies have suggested that patients with normal-pressure glaucoma may have low cerebrospinal fluid pressure [19–21]. Our findings appear to further support the hypothesis that low retrobulbar cerebrospinal fluid pressure plays a role in the pathogenesis of normal-pressure glaucoma-like optic disc changes.

There are 2 distinct types of craniopharyngiomas based on the histological patterns: adamantinomatous craniopharyngiomas (ACP) characterized by activating CTNNB1 mutations [22,23] and papillary craniopharyngiomas characterized by BRAFv600E mutations [24]. Virtually all craniopharyngiomas in children are of the ACP type, whereas adult craniopharyngiomas are primarily papillary. The different patterns of changes in GCC and pRNFL observed between child and adult patients in our study might be associated with the distinct pathogenesis of these 2 types of craniopharyngiomas. Further in-depth studies with larger sample sizes need to be performed to confirm such speculation.

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Conclusions

The current study showed that craniopharyngiomas leads to significant GCC and pRNFL thinning compared to that in controls and that measuring segmented layers of the retina divided in quadrants provides adequate quantitative data for differentiating diseased eyes from normal controls. It also showed that segmented macular GCC thickness measurement was more sensitive than pRNFL in detecting optic nerve damage in the eyes of craniopharyngioma patients, and was especially useful in the diagnosis of childhood craniopharyngioma. In addition, a thinner pRNFL was found to be correlated with VCDR in child craniopharyngioma patients, indicating that it might be clinically useful in assessing optic nerve damage associated with childhood craniopharyngioma.

Conflict of interests

None.

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