• Clinical Research •

Detection of macular ganglion cell complex loss and correlation with choroidal thickness in chronic and recurrent central serous chorioretinopathy

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Abstract

● **AIM:** To investigate the association of ganglion cell complex thickness (GCCt), global loss volume percentage (GLV%), and focal loss volume percentage (FLV%) with structural and functional findings among patients with chronic central serous chorioretinopathy (CCSC) and recurrent central serous chorioretinopathy (RCSC) by optical coherence tomography (OCT).

● **METHODS:** Among 29 patients with monocular affected central serous chorioretinopathy (CSC), 15 had CCSC, and 14 had RCSC. The GCCt, FLV%, GLV%, and subfoveal choroidal thickness (SFCT) and sublesional choroidal thickness (SLCT) values were determined using OCT, and the association of these characteristics with neural structure parameters, choroidal morphology, features and functional alterations were estimated for the CCSC and RCSC patients.

● **RESULTS:** In CCSC, the affected eyes had significantly lower GCCt values than the fellow eyes in the macular regions (all $P<0.05$), with the highest GCCt observed in the inferior area. A significant association was found between the GCCt in different regions and the change in best corrected visual acuity (BCVA; r=-0.696; -0.695; -0.694, $P<0.05$) in CCSC patients. A statistically significant moderate negative correlation indicated that long-term CCSC was associated with greater differences in the GCCt in different regions between affected and fellow eyes (r=-0.562; r=-0.556; r=0.525, $P<0.05$). Additionally, observation of thickened SFCT was associated with a worse FLV% (r=0.599; r=0.546, $P<0.05$) in both groups. Similarly, thickened SLCT was associated with FLV% in RCSC patients (r=0.544, $P<0.05$).

● **CONCLUSION:** The distribution and GCCt are associated with the duration and visual outcomes of CCSC, whereas there is no correlation among RCSC patients. FLV% may be instrumental in differentiating the various outer choroidal vessels (pachyvessels) in long-term CSC. These results suggest that neural structure parameters may aid in estimating and predicting the recovery of altered morphology and function in CCSC and RCSC patients.

● **KEYWORDS:** ganglion cell complex parameters; choroidal thickness; optical coherence tomography; central serous chorioretinopathy

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INTRODUCTION

Central serous chorioretinopathy (CSC) is a chorioretinal disease characterized by limited serous detachment of the neurosensory retina at the posterior pole, often associated with varying degrees of low-grade focal leakage at the level of the altered retinal pigment epithelium (RPE)[1-3]. These histological, structural, and vascular abnormalities lead to clinical symptoms such as micropsia with a partial reduction in visual acuity and mild colour discrimination[4-6]. This condition is predominantly seen in middle-aged males[7]. In light of recent discoveries, most risk determinants of CSC now include male sex, alcohol consumption, smoking, higher education level, shift work, hypercortisolism and so on[8-13].

The exact aetiology and pathogenesis of CSC have not been

elucidated[14]. Mechanistic research remains a significant challenge and warrants further investigation. Venous overload or choroidal arteriovenous anastomoses have been proposed as a new hypothesis for the pathogenesis of CSC[15-16].

In a considerable proportion of CSC cases, the structural damage continues to increase in severity with disease progression despite the administration of treatment. If spontaneous resolution reveals subretinal fluid (SRF) and/or single RPE detachment does not occur, the disease can still recur and/or becomes chronic (often more than 6mo), and the effectiveness of further treatment options will be diminished[17]. Both chronic CSC (CCSC) and recurrent CSC (RCSC; an episode of acute CSC following a previous episode with complete subretinal detachment resolution) frequently results in severe irreversible vision damage due to photoreceptor impairment and RPE atrophy.

Recently, increasing attention has been given to macular ganglion cell loss [ganglion cell complex (GCC): a composite of the inner plexiform layer (IPL), ganglion cell layer (GCL), and nerve fibre layer] in retinal diseases, and GCC-associated values have been suggested as a more sensitive marker of potential inner retinal thinning than the retinal neural fibre layer height[18]. Demirok *et al*[2] found that the ganglion cell complex thickness (GCCt) was significantly reduced in both acute and chronic CSC relative to that of healthy subjects. Similar results by Jaisankar *et al*[19] showed a reduction in retinal layer thickness in both acute and recurrent CSC groups. However, other than these studies on the outer retinal layer and pachychoroid in CSC, few studies have investigated the function or histology of GCC structures and their correlations with the subfoveal choroidal thickness (SFCT) and sublesional choroidal thickness (SLCT) in chronic or recurrent cases.

The introduction of spectral-domain optical coherence tomography (SD-OCT) has allowed the acquisition of neural structure parameters, providing a quantitative assessment of the inner retinal layer morphology. Enhanced depth imaging optical coherence tomography (EDI-OCT) has allowed deeper visualization of the choroid, providing newer insights into the microstructure of the retina and choroid and enabling the assessment of manual measurements of the SFCT and SLCT.

This study aimed to assess and compare macular GCC parameters between the affected eyes and fellow eyes in CCSC and RCSC patients and to investigate the presence of factors correlated with altered best corrected visual acuity (BCVA) and disease duration (period since the first onset of symptom) in conjunction with these clinical quantitative assessment findings. Additionally, the correlations between changes in the SFCT and SLCT and the GCCt, focal loss volume percentage (FLV%), and global loss volume percentage (GLV%) were also evaluated in the two groups.

SUBJECTS AND METHODS

Ethical Approval This retrospective study was approved by the Ethical Review Committee of Tianjin Eye Hospital (protocol No.2022012/February 24, 2022) and adhered to the provisions of the Declaration of Helsinki for research involving human subjects. After the purpose and procedure of the study were explained, all the subjects signed written informed consent forms.

Inclusion and Exclusion Criteria CCSC patients aged between 19-66y in the outpatient department of Tianjin Eye Hospital from March 2022 to May 2022 were enrolled. Patients with primary, monocular onset CCSC and RCSC and an unaffected fellow eye were eligible to participate. The fellow eyes were included as the control group. Ophthalmic examinations were performed for all CSC patients, including visual acuity, slit-lamp biomicroscopy, direct ophthalmoscopy, colour fundus imaging and fundus fluorescence angiography and/or indocyanine green angiography (ICGA; Heidelberg Engineering, Heidelberg, Germany). CCSC patients were diagnosed based on the results of clinical evaluation and structural OCT, fundus fluorescein angiography (FFA), and ICGA imaging.

Multimodal imaging from the right eye of Case 1, a patient with CCSC, and from the left eye of Case 2, a patient with RCSC, are shown in Figures 1 and 2, respectively. One of the inclusion criteria for these patients was persistent subretinal fluid involving the macula for at least 6mo or serous retinal detachment with diffuse atrophy and decompensation of the RPE (also referred to as diffuse retinal pigment epitheliopathy) with/without gradual, indistinct RPE leakage on FFA[20]. RCSC included findings with no severe RPE changes on FFA compared with CCSC and a leaking pattern consistent with acute CSC but with an apparent history of recurrence[21].

The exclusion criteria was as follows: 1) other fundus diseases, such as retinal vein occlusion, diabetic retinopathy, Vogt-Koyanagi-Harada, optic disc pits, and scleritis; 2) a history of eye surgery, including laser therapy or intravitreal injections; a history of trauma or surgery (especially kidney, heart, and bone marrow transplantations[22]) within 6mo; hypertension, alcohol, tobacco, corticosteroids, MEK inhibitors, Cushing syndrome, or steroid use; and a history of disorders that can cause serious macular detachment and cystoid degeneration; and 3) lesions with extramacular involvement beyond the measurement range of the GCC on OCT.

Spectral Domain Optical Coherence Tomography and Optical Coherence Tomography Angiography An RTVue XR OCT instrument (Model RT-100, ver.4.0, Fremont, California, USA) was used to determine the thickness of the GCC with a capture rate of 26 000 axial scans (A-scans) per second and a 5 μm depth resolution in tissue[23]. The GCCt

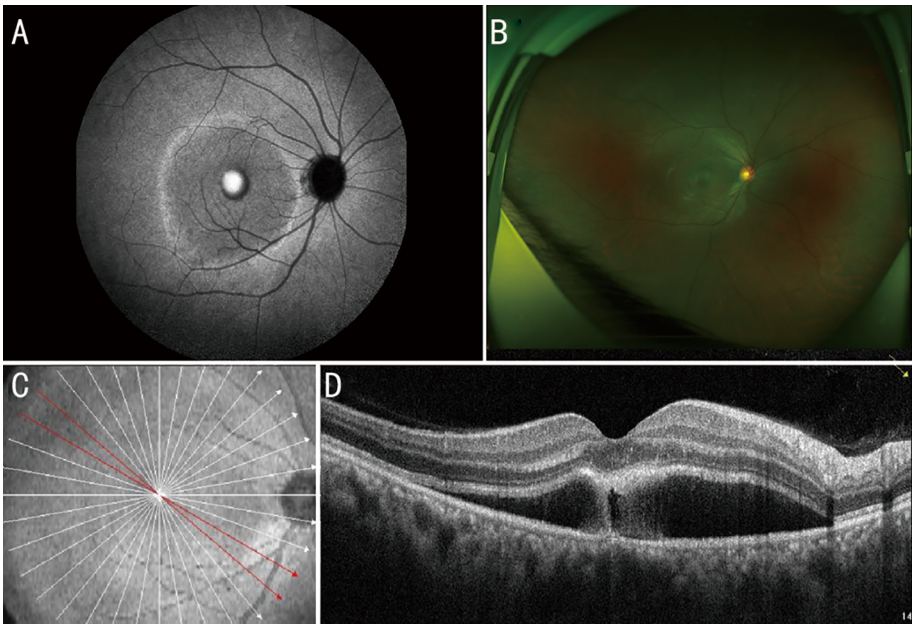

Figure 1 Multimodal imaging from right eye of a patient affected by CCSC A: The late-phase ICGA shows hyperfluorescent areas; B: The fundus photography was performed with the wide field scanning ophthalmoscope persists SRF marked as a bleb at the center of macula; C: Fundus photography show scanning lines (red arrows); D: Structural OCT images demonstrate acorresponding SRF. No vascular abnormalities were evident on the OCT. CCSC: Chronic central serous chorioretinopathy; ICGA: Indocyanine green angiography; SRF: Subretinal fluid; OCT: Optical coherence tomography.

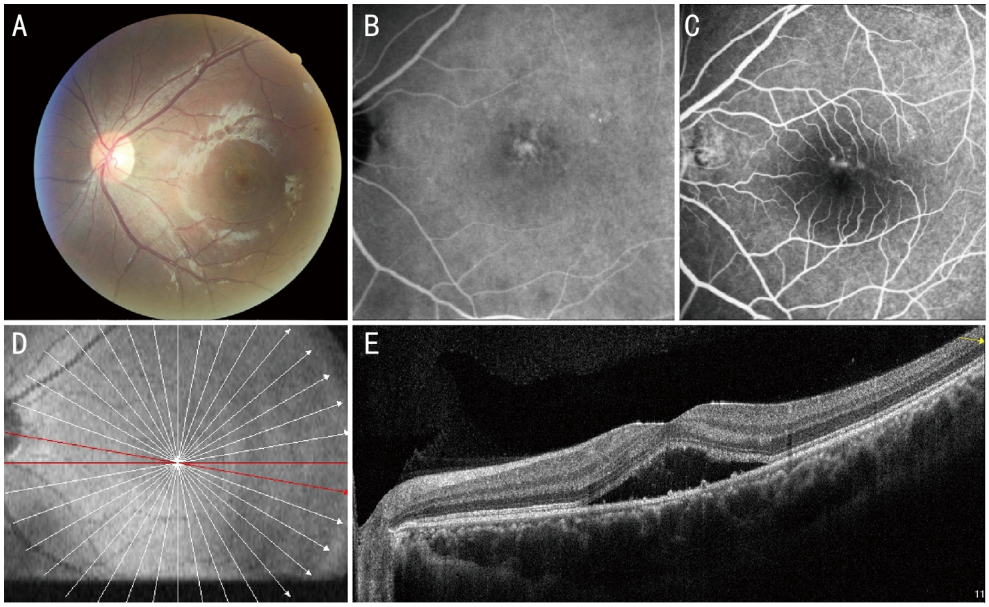

Figure 2 Multimodal imaging in an RCSC case A: CFP displays the presence of neurosensory detachment in the centeral region of the macula; B: Early-phase fluoresce in angiography of the left eye shows hyperfluorescent areas in central region of the macula; C: Late-phase ICGA the same eye displays hyperfluorescent regions because of choroidal permeability; D: OCT image of the left eye fundus photography show scanning lines (red arrows); E: OCT image displays the presence of PED and neurosensory detachment in the same region of the macula. RCSC: Recurrent central serous chorioretinopathy; CFP: Color fundus photo; ICGA: Indocyanine green angiography; OCT: Optical coherence tomography; PED: Pigment epithelium detachment.

was analysed from the internal limiting membrane to the outer boundary of the inner plexiform layer and along 15 vertical lines and one horizontal line, mapping a wide area (7 mm^2) centred 1 mm temporal to the fovea, enabling the GCC status to be observed. The GCC scan data were displayed as a thickness map of the GCC layer. On the GCCt map, the GLV is used to measure the sum of the negative fractional deviation of the entire area. The FLV (in volume) provides the percentage of significant tissue loss for the volume and generates a thickness value "pattern map" with respect to the average pattern map from an

Table 1 Demographic and clinical characteristics of the study

Parameters	CCSC group (*n*=15) (min–max)		RCSC group (*n*=14) (min–max)		*P*		
	Affected eye	Fellow eye	Affected eye	Fellow eye	CCSC *vs* RCSC (affected eye)	CCSC[c]	RCSC[c]
Age, y, mean±SD	35.3±10.3 (19-66)		35.1±10.4 (21-59)		0.949[a]		
Sex (female/male), *n* (%)	2 (15.3)/13 (84.6)		2 (16.6)/12 (83.3)		0.847[b]		
BCVA, mean±SD (logMAR)	0.6±0.1 (0.3-0.9)	0.9±0.1 (0.8-1.00)	0.5±0.1 (0.4-0.8)	0.9±0.1 (0.7-1.00)	0.988[a]	0.034[d]	0.012[d]
Refractive error (SE, D)	1.43±2.05	1.29±2.17	1.44±1.03	1.54±1.23	0.456[a]	0.396[a]	0.236[a]
IOP (mm Hg)	14.5±3.4	16.3±3.4	16.6±2.8	17.7±2.0	0.123[a]	0.345[a]	0.218[a]
Symptom duration in months, median (range)	9 (6-16)		16 (5-96)		0.041[d]		
PED (OCT)	10/15		8/12		0.061[b]		

CCSC: Chronic central serous chorioretinopathy; RCSC: Recurrent central serous chorioretinopathy; BCVA: Best-corrected visual acuity; logMAR: Logarithm of the minimum angle of resolution; SE: Spherical equivalent; D: Diopter; IOP: Intraocular pressure; OCT: Optical coherence tomography; PED: Pigment epithelium detachment; VA: Visual acuity. [a]Independent *t*-test; [b]Chi-square test for qualitative data between groups; [c]Affected eye *vs* fellow eye; [d]Statistical significant.

Table 2 GCC parameters of CCSC and RCSC

Parameters	CCSC (*n*=15)		RCSC (*n*=14)		*P*		
	Affected eye	Fellow eye	Affected eye	Fellow eye	CCSC *vs* RCSC (affected eye/fellow eye)	CCSC[a]	RCSC[a]
Average GCC thickness (μm)	109.93±9.43	120±15.17	110.71±9.47	115.21±17.61	0.826/0.867	0.023[b]	0.310
Superior GCC thickness (μm)	106.87±7.69	117.20±13.82	106.64±8.17	111.64±13.75	0.103/0.123	0.005[b]	0.103
Inferior GCC thickness (μm)	113.13±14.08	127.33±21.39	115.00±14.02	121.35±24.38	0.310/0.279	0.029[b]	0.310
FLV%	0.98±1.06	0.94±1.10	0.68±0.79	0.64±0.83	0.621/0.601	0.619	0.621
GLV%	1.09±1.09	1.04±1.15	0.80±0.86	0.75±0.92	0.768/0.713	0.767	0.768

GCC: Ganglion cell complex; CCSC: Chronic central serous chorioretinopathy; RCSC: Recurrent central serous chorioretinopathy; GLV%: Global loss volume percentage; FLV%: Focal loss volume percentage. [a]Affected eye *vs* fellow eye; [b]Statistical significant.

age-matched normative database[24-25]. Thus, the FLV is used to measure focal loss, whereas GLV represents the pattern of diffuse loss[26].

At least two retinal experts assessed and measured the SFCT and SLCT both horizontally and vertically, and the average of their results was recorded as SFCT or SLCT. The choroidal thicknesses were assessed by manual measurements of the distance between the hyperreflective band corresponding to Bruch's membrane and the choroidal-scleral interface below the foveola or below the centre of a pachychoroid lesion assisted by FFA or ICGA images (Figure 3). We accepted only scans with high image quality [signal strength index (SSI) >-60]. The measurements of GCCt were compared with values from a normative database. The device software then produced a colour-coded GCCt map.

Superficial and deep capillary plexuses was then measured in optical coherence tomography angiography (OCTA) scans using commercial software available from RTVue XR

All the values measured in this study were obtained before the current treatment session to rule out the effect of laser treatment on ganglion cell complex analysis and symptoms.

Statistical Analysis Statistical analysis was performed using the Statistical Package for Social Sciences (version 17.0, SPSS Inc., Chicago, IL, USA). For statistical comparison, data are expressed as the mean±standard deviations. The Shapiro-Wilk test was used to determine the normality of counting variables before analysis; comparisons of nonnormally distributed variables between groups were assessed with the Mann-Whitney *U* test was used. The Kolmogorov-Smirnov test was used to assess the normality of the distributions of FLV% and GLV%, and the independent sample *t* test was used for comparison between the two groups. The paired *t* test was used to compare the affected and fellow eyes within groups. The Chi-square test was used to compare qualitative data between groups.

Correlations between two quantitative variables were assessed by using Pearson's correlation coefficient. The correlation coefficient ranges from 0 to 1, and the corresponding correlation can be classified as weak (*r*: 0-0.24), fair (*r*: 0.25-0.49), moderate (*r*: 0.5-0.74), and strong (*r*: 0.75-1). $P<0.05$ indicates the existence of a statistically significant difference.

RESULTS

Overall, our analysis included 29 subjects (15 had CCSC and 14 had RCSC), and there were 25 males and 4 females. All of the demographic and clinical characteristics of the CCSC and RCSC groups are shown in Table 1.

The BCVAs in the two groups were significantly different between the affected and fellow eyes ($P<0.05$). The duration of the condition between the two groups was statistically significant, while the other demographic and clinical characteristics matched well between the two CSC groups.

There were no statistically significant differences in the GCC values between the CCSC and RCSC groups. Among the CSC patients, affected eyes had significantly lower GCCts than fellow eyes in the macular regions (all $P<0.05$), with the highest thickness in the inferior area. The neural structure parameters of the CCSC and RCSC groups are presented in Table 2. No significant difference was found in the comparison of other parameters ($P>0.05$; Figure 4).

The changes in the BCVA in the CCSC and RCSC groups was 0.14±0.19 and 0.07±0.17, with ranges of -0.2 to 0.5 and

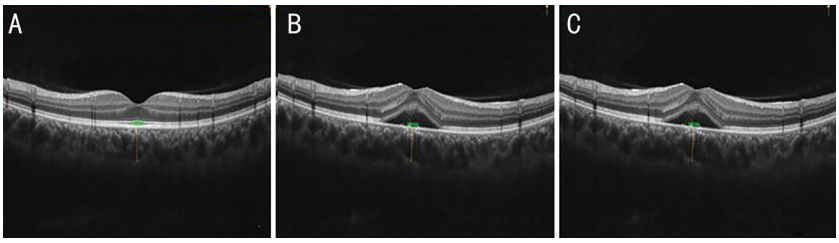

Figure 3 Choriodal thicknesses were calculated as the distance between Bruch's membrane and choroidal-scleral interface at the fovea The yellow line shows the measurement of SFCT (defined as the hyper-reflective band corresponding to Bruch's membrane and the choroidal-scleral interface below the foveola below the center of a pachychoroid lesion). OCT shows he fellow healthy eye (A), SRF at fovea (B) and a pachychoroid lesion (C) at the time of the initial consultation (the foveola and centre position in this case is very close). SFCT: Subfoveal choroidal thickness; SRF: Subretinal fluid; OCT: Optical coherence tomography.

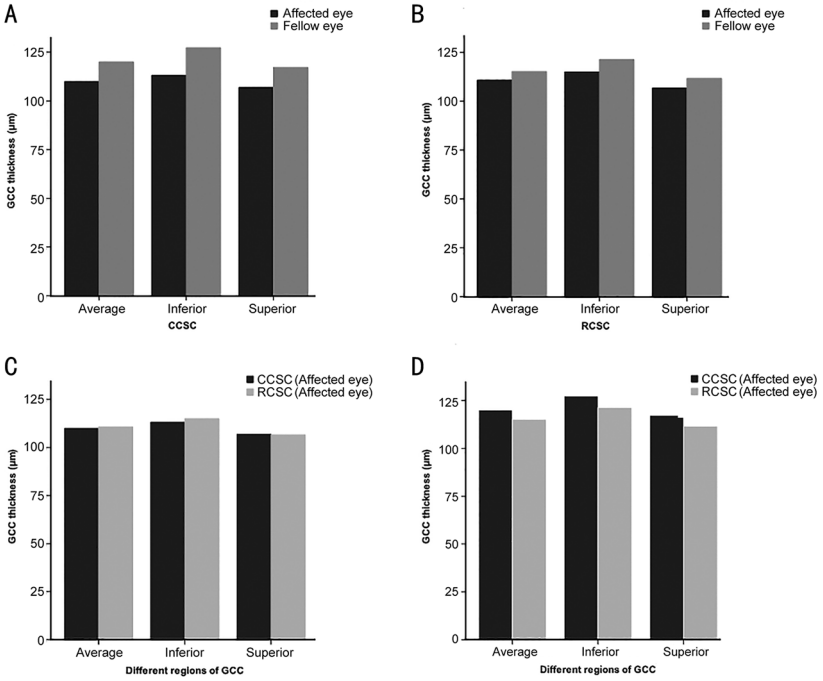

Figure 4 GCC thickness compared in different ways in CCSC and RCSC GCC thickness variables of affected and fellow eyes in CCSC (A) and RCSC (B). In the CCSC group, affected eyes had significantly thinner GCC thickness than fellow eyes in all macular regions (all $P<0.05$). Comparation of different region GCC thickness affected eyes (C) and fellow eyes (D) between CCSC and RCSC (all $P>0.05$). GCC: Ganglion cell complex; CCSC: Chronic central serous chorioretinopathy; RCSC: Recurrent central serous chorioretinopathy.

-0.2 to 0.4, respectively. The changes were not statistically correlated with the durations of either CCSC or RCSC ($P>0.05$).

Multivariable analysis was completed to estimate the effect of neural structure parameters and their derivative indices, such as FLV% and GLV%, in the changes of BCVA in CCSC. A significant association was found between the GCCt of all regions in CCSC and the changes in BCVA ($P<0.05$, r=-0.696, -0.695, -0.694), as shown in Table 3. Conversely, the FLV% and GLV% were not correlated with the altered BCVA ($P>0.05$).

A significant moderate negative correlation was found between the whole image GCCt (for the average, superior and inferior GCCt) and the duration of CCSC, as seen in Table 4.

These correlations indicate that a longstanding duration of CCSC is associated with higher differences in the GCCt between affected and fellow eyes. We further analysed both the CCSC and RCSC groups, and observation of a larger SFCT

Table 3 The effect of GCC thickness, FLV%, GLV% and duration of CSC on variety BCVA in CCSC and RCSC

Parameters (affected eye)	*r* (CCSC/RCSC)	*P* (CCSC/RCSC)
Average GCC thickness (μm)	-0.696/0.114	0.004[a]/0.697
Superior GCC thickness (μm)	-0.695/-0.239	0.005[a]/0.411
Inferior GCC thickness (μm)	-0.694/0.176	0.004[a]/0.548
FLV%	0.231/-0.093	0.407/0.751
GLV%	0.239/-0.028	0.390/0.924

CCSC: Chronic central serous chorioretinopathy; RCSC: Recurrent central serous chorioretinopathy; GCC: Ganglion cell complex; GLV%: Global loss volume percentage, FLV%: Focal loss volume percentage; BCVA: Best-corrected visual acuity. [a]$P<0.05$ was considered statistically significant.

Table 4 Association between durations of CSC and GCC parameters (differences) in the CCSC and RCSC groups

Parameters (affected eye)	CCSC group (*n*=15)	RCSC (*n*=14)	*r* (CCSC/RCSC)	*P* (CCSC/RCSC)
Average GCC thickness (μm)	109.93±9.43	110.71±9.47	-0.149/0.157	0.596/0.591
Superior GCC thickness (μm)	106.87±7.69	106.64±8.17	0.157/-0.130	0.567/0.657
Inferior GCC thickness (μm)	113.13±14.08	115.00±14.02	-0.309/0.225	0.263/0.439
FLV%	0.98±1.06	0.68±0.79	0.196/0.035	0.485/0.907
GLV%	1.09±1.09	0.80±0.86	0.196/-0.012	0.485/0.967
Parameters of difference[a]				
Average GCC thickness (μm)	-10.07±15.26	-4.50±15.94	-0.562/-0.093	0.029[b]/0.842
Superior GCC thickness (μm)	-10.33±12.12	-5.00±10.68	-0.556/-0.093	0.031[b]/0.751
InferiorGCC thickness (μm)	-14.2±22.55	-6.36±22.51	-0.525/-0.052	0.044[b]/0.860
FLV%	0.05±0.35	0.05±0.36	-0.154/-0.137	0.606/0.640
GLV%	0.05±0.63	0.05±0.65	0.059/0.083	0.842/0.778

CCSC: Chronic central serous chorioretinopathy; RCSC: Recurrent central serous chorioretinopathy; GCC: Ganglion cell complex; GLV%: Global loss volume percentage; FLV%: Focal loss volume percentage. [a]Difference value of affected eyes and fellow eyes GCC thickness; [b]*P*<0.05 was considered statistically significant.

Table 5 Relationship between GCC parameters and SLCT in CCSC and RCSC groups (r/*P*)

Parameters (affected eyes)	CCSC group (*n*=15)	RCSC group (*n*=14)
Age (γ)	0.012/0.996	0.375/0.155
BCVA (affected eyes)	-0.02010582	0.020/0.946
Duration of CSC (mo)	0.331/0.228	-0.401/0.148
Average GCC thickness (μm)	0.104/0.713	-0.407/0.186
Superior GCC thickness (μm)	0.097/0.730	0.237/0.414
Inferior GCCthickness (μm)	0.087/0.759	0.363/0.203
FLV%	0.421/0.118	0.544/0.044[a]
GLV%	0.182/0.517	0.097/0.743

CCSC: Chronic central serous chorioretinopathy; RCSC: Recurrent central serous chorioretinopathy; GCC: Ganglion cell complex; GLV%: Global loss volume percentage; FLV%: Focal loss volume percentage. [a]*P*<0.05 was considered statistically significant.

was related to a worsened FLV% (*P*<0.05). A similar result was found for the SLCT assessment in the RCSC group (Tables 5, 6).

The OCTA examination was performed in some patients (8 eyes in CCSC and 8 eyes in RCSC): the average vessel density (%) in the whole image of superficial retinal capillary plexus (SVD) and deep retinal capillary plexus (DVD) were severally 46.66±4.78, 47.75±3.85 and 46.43±3.76, 47.47±4.23 in CCSC and RCSC cases. It was a moderate negative correlation between SVD and FLV% in CCSC and RCSC patients (*r*=-0.62; -0.68, *P*<0.05), however, the other parameters have no correlation.

DISCUSSION

In several symptomatic CSC patients, the RPE and choroid do not heal well, and even if the SRF disappears, 5% of patients still experience structural integrity and diffuse transport dysfunctions of the RPE and choroid, limiting visual improvement[27]. Therefore, we focused on the functional and histological structure of the detached retina and assumed that the serious circumstances could be due not only to circulatory disturbances in the retinal and choroidal layers but also to ganglion cell dysfunction based on the nature of the detachment.

We detected a significantly lower GCCt in the affected eyes than in the fellow eyes among the CCSC patients. Since neurons are the most fragile and demanding cellular elements in the GCC, it is conceivable that when the RPE or detachment drastically changes the microenvironment composition, the GCC is the primary element affected[28-29].

The pachychoroid spectrum was the first named hypertrophic choroidal disease in ophthalmology; given the intrinsic choroidal abnormalities present in this spectrum, the choriocapillaris over the large choroidal vessels may have limited elasticity or compliance for adjustment in CSC[30]. Several authors have investigated vascular deteriorations such as choroidal hyperpermeability that result in pachychoroid[31-32]. Imbalanced levels of neurodegenerative biomarkers such as vascular endothelial growth factor (VEGF), which is mainly localized in the cytoplasm of the RGCL and the IPL, and pigment epithelium-derived factor (PEDF), which is involved in neuronal differentiation in the retina, have been implicated in the development of CSC by increasing vascular permeability[33]. In agreement with the immunolocalization, cells in the RPE, ganglion cell layer, and choroid were also related to PEDF or anti-VEGF in adult retina[34-35]. These neurodegenerative biomarkers affect the composition of and metabolic changes in the GCC in CSC. In particular, a long-term, persistent disease course strengthens the effect of GCC thinning. Interestingly, the neural structural parameters were not found to be statistically associated with any of the detected relevant factors in RCSC. Prolonged reattachment within several months or years of onset is considered a relevant factor associated with photoreceptor atrophy[36]. It has been postulated

Table 6 Relationship between GCC parameters and SFCT in CCSC and RCSC groups *r*/*P*

Parameters	CCSC group (*n*=15)		RCSC group (*n*=14)	
	Affected eye	Fellow eye	Affected eye	Fellow eye
Age (y)	-0.420/0.119	-0.334/0.223	0.379/0.181	-0.276/0.34
BCVA (affected eyes)	-0.243/0.384	-0.188/0.501	0.003/0.993	-0.138/0.638
Durations of CSC (mo)	0.021/0.941	0.002/0.993	-0.300/0.297	-0.189/0.519
Average GCC thickness (μm)	0.466/0.080	0.418/0.121	0.481/0.018	0.385/0.174
Superior GCC thickness (μm)	0.097/0.730	0.436/0.105	0.386/0.173	0.335/0.242
Inferior GCCthickness (μm)	0.236/0.397	0.425/0.115	0.437/0.118	0.466/0.093
FLV%	0.599/0.018[a]	-0.182/0.516	0.546/0.043[a]	-0.153/0.601
GLV%	0.207/0.458	-0.138/0.623	0.309/0.282	-0.214/0.464

CCSC: Chronic central serous chorioretinopathy; RCSC: Recurrent central serous chorioretinopathy; GCC: Ganglion cell complex; GLV%: Global loss volume percentage; FLV%: Focal loss volume percentage. [a]*P*<0.05 was considered statistically significant.

that the inner retinal layer in CCSC is affected by choroidal hyperpermeability and an associated increase in pachychoriod and thus may be more complex and variable than that in RCSC.

Furthermore, previous studies have indicated that retinal and choroidal blood flow is varied when the retina is detached[37-38]. The superficial capillary plexus (SCP) is primarily located within the ganglion cell layer. A significant reduction in SCP vessel density has been found in the loss of ganglion cells[39]. We found that SCP flow density was inversely associated with FLV in a proportion of patients with CCSC and RCSC. We postulated that the decreasing signal intensity within the choroid may be influenced by haematologic and pathological changes, such as changes in subretinal fluid and RPE detachment. Mechanical compression by the pachychoroidal trait would compress the SCP and cause ischaemia and apoptosis in the GCL. Moreover, the effect of GCC layer thinning on the loss of visual function and its changes in longstanding duration is well documented in CCSC. Because of the dilated vortex veins or anastomotic vessels, the inner choroid becomes thinner in CSC. Due to this morphologic change, especially in the macular area, ischaemia of the inner choroid results in high metabolic activity. In Foo *et al*'s[40] study, the relationship of Haller's and Sattler's layers with visual acuity was a marker of photoreceptor health and visual prognosis. GCCt thinning appears to result in anterograde or retrograde axonal loss[41]. Retinal circuits transform the pixel representation of photoreceptors into the feature representations of ganglion cells, whose axons, bodies and dendrites transmit these representations to the brain and contribute to a variety of visual perception effects[42]. Neurons are extremely sensitive to oxidative stress damage, and an imbalance in reactive oxygen species is often involved in CSC as one of the postulated pathogeneses[38,43-44]. CSC patients have a low arterial blood flow velocity and blood flow volume in the posterior ciliary artery, and circulation from the ophthalmic artery to the choriocapillaris is impaired, probably suggesting poor choroidal blood perfusion[45]. In persistent cases, there is critical oxidative stress damage due to the haemodynamics and hypoperfusion of the choriocapillaris as well as choroidal lobular ischaemia and venous congestion. Oxidant damage can induce mitochondrial stress and apoptotic cell death in tissues soon after the onset of CSC and impose a continuous effect on mitochondrial metabolic activity. Consequently, long-term oxidative effects caused by abnormal choroid and retinal blood flow lead to damage to the microstructure and visual function.

In addition, the fellow eyes of CSC patients had a larger flow void area of the choriocapillaris and a thicker choroid related to dilatation of the choroid layer, mainly the Haller layer vessels, than those of healthy controls[46-47]. More than 60% of the unaffected fellow eyes in CSC patients demonstrate choroidal hyperpermeability[48-49]. Similar structural damage could occur in the fellow eye, and the thinning GCCt of these eyes in the long term might contribute to reducing the differences in the GCCt; the interindividual variation in the inner retinal neural structure and vascular circulation has a large impact on the differences in the GCCt. Thus, the above factors might be the reason that the GCCt was associated with changes in the BCVA or the duration of CCSC.

It would be of clinical benefit to use neural structure parameters and derivative indices for assessment and prognostic observation indices in persistent or recurrent CSC, primarily because these quantitative and pattern-based measurements revealed a structure–function relationship between the affected and fellow eyes, particularly the added factor of the choroidal thickness.

Our study was the first to exhibit higher FLV% values in CSC patients with dilated choroidal vessels. The specific reasons for this result remain unknown, but the following explanations may aid in uncovering the true mechanisms: first, the pattern parameters were more sensitive or more specific than those of the GCCt[50]; second, the FLV% and GLV% were obtained

from the calculation of the GCC loss volume with differing levels of formality; specifically, if the reduction in the GCCt was uneven, the FLV% would have been elevated. It is worth noting that the choroid blood flow density is differentially regulated in the choriocapillaris, Sattler's, and Haller's layers, as it is the choroid vascular density that causes the disproportionate formation of pachyvessels. Thus, choroidal vasculature remodelling at the posterior arteriovenous anastomosis is randomly distributed throughout the choroidal layers, indicating that the morphology of the choroid becomes more complicated and confusing. Hence, FLV% could reflect changes in the SFCT or SLCT. The latter two as important parameters in choroidal disease, especially, in the evaluated observations before and after treatment[51-52]. Whether the relationship between GCC and the two can indicate the treatment effect of CSC and RCSC is also a topic that can be discussed in the future.

Several limitations associated with our study need to be considered. First, the present study did not include patients with healthy eyes. Furthermore, we focused on the long-term and recurrent CSC, and the GCC parameters might have been altered in the fellow eyes; these points should be addressed in future studies. Moreover, the sample size was relatively small. A future study with a larger sample size of both CSC and healthy participants should be conducted. Finally, longer follow-up for the CCSC and RCSC participants should be conducted to further validate the results of our study.

In summary, thicken choroidal thickness was associated with more obvious FLV loss, and the GCCt was correlated with the duration of and BCVA changes in CCSC, which were shown to have meaningful results in the present SD-OCT study. One of the major strengths of the present study was the demonstration of GCC thinning to a certain extent and that the vision loss could not recover in patients with long-term CSC. Evaluation of the FLV may help in patient prognosis and in the estimation of the degree of pachyvessel changes in CCSC and RCSC. Our findings may indicate a relatively predisposing influence of alterations in the inner retinal neural structure on CSC.

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