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The relation of the serum aldosterone level and central serous chorioretinopathy – a pilot study

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Abstract. – OBJECTIVE: The aim of this study was to investigate the serum aldosterone level and abnormal levels of mineral corticoid in patients with the central serous chorioretinopathy (CSC).

PATIENTS AND METHODS: All recruited patients with CSC received fundus fluorescein angiography (FFA), enhanced depth imaging spectral-domain optical coherence tomography (EDI-OCT) and serum aldosterone assay. The patients were classified into spontaneously resolved group and unresolved group according to a 3-months follow-up of Optical Coherence Tomography (OCT) examination. Patients from unresolved group were recruited to receive treatment with 40 mg spironolactone orally for 2 months. After the treatment, the EDI-OCT and best corrected visual acuity (BCVA) were performed again to assess the treatment efficacy.

RESULTS: The study included 61 patients (72 eyes) with 34 patients in the unresolved group and 27 patients in the resolved group. The aldosterone level was significantly associated with the subfoveal choroidal thickness (SFCT) of revolved CSC eyes (r=0.342, $p<0.05$) as well as the SFCT of unresolved CSC eyes (r=0.348, $p<0.05$). And the aldosterone level in the unresolved CSC group was greater than that in the spontaneously resolved group (161.8 ± 50.1 ng/dl vs. 122.5 ± 50.5 ng/dl, $p<0.05$). The central macular thickness and SFCT were decreased significantly ($p<0.05$) after the treatment with 40 mg/d spironolactone for two months.

CONCLUSIONS: The unresolved CSC patients were characterized by high level of aldosterone and thickened SFCT. Spironolactone treatment was associated with the improvement of chronic CSC. Besides, the side effect of spironolactone treatment was rare.

Key Words:
Central serous chorioretinopathy, Serum aldosterone level, Spironolactone, Subfoveal choroidal thickness.

Introduction

Central serous chorioretinopathy (CSC) is a common disease of the retina characterized by serous detachment of neurosensory retina, retinal pigment epithelial (RPE) in the periphery and choroidal hyper-permeability as demonstrated by fluorescence indocyanine green angiography[1,2]. The occurrence of this disease is about 1/10000[3] and mostly in mid-aged males[4]. Generally, acute CSC is known to resolve spontaneously in 60% of patients within 3 months. However, some patients have persistent retinal detachment which may lead to irreversible visual impairment[5]. Although the pathogenesis of the disorder is not precisely known, it is generally believed that the glucocorticoid and adrenergic hormones may affect the retinal pigment epithelium (RPE) and the choroid, and play an important role in the pathophysiology of CSC[3,4].

The thickened choroid and the choroidal hyperpermeability found by the EDI-OCT[6,7] and indocyanine green angiography may prove the assumption that the subretinal fluid accumulation and retinal detachment are caused by hemodynamic changes in the choroid[8-10]. Recently, Zhao et al[11] proved that the mineralocorticoid receptor is expressed in rat choroidal vasculature, and the glucocorticoid is bound to the mineralocorticoid receptor (MR) which leads to CSC. Additionally, mineralocorticoid hormones are synthesized by adrenal cortex as well as glucocorticoid[12]. Excessive MR occupancy by mineralocorticoid also leads to CSC. Besides, mineralocorticoid, such as aldosterone, contributes to hypertension[13,14] as a known risk factor for CSC[15-17].

Herein, we investigated whether there was evidence of abnormal levels of mineral corticoid in

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CSC patients that played an important role in the pathophysiological process of CSC.

Patients and Methods

Study Design and Patients

This was a combination of cohort study and single arm clinical trial. The study included 72 eyes of 61 patients (50 men and 11 women) with CSC, who were examined during August 2013 and July 2014 in Ophthalmology Department, First Affiliated Hospital of Nanjing Medical University (Nanjing, Jiangsu, China).

CSC was diagnosed by fundus fluorescein angiography (FFA) showing a focal leak at the level of the RPE. A subretinal detachment of the retinal photoreceptors from the RPE layer was demonstrated by spectral-domain OCT. The inclusion criteria of patients including all aged ≥18 years old; existence of subretinal fluid (SRF) with subjective symptoms such as decreased vision or metamorphopsia. All patients received a complete ophthalmic examination at the initial visits, including best-corrected visual acuity measurement, slit-lamp biomicroscopy, fluorescein angiography and spectral-domain OCT. All patients received consecutive follow-up SD-OCT examinations. The serum aldosterone concentration was obtained immediately after the diagnosis of CSC, which was determined by radioimmunoassay.

Exclusion criteria included current pregnancy, the history of taking corticosteroids or related medications, systemic diseases such as endogenous hypercortisolism, and diabetes mellitus. Macular disorders such as idiopathic choroidal neovascularization, polypoidal choroidal vasculopathy, and age-related macular degeneration were excluded from this study. In addition, the eyes with a history of previous treatment, including macular photocoagulation, photodynamic therapy, or intravitreal anti VEGF injection, were also excluded. This study was approved by the Ethics Committee of First Affiliated Hospital of Nanjing Medical University. The informed consent was signed by all patients voluntarily.

Spectral-Domain OCT Measurements

Patients were imaged by spectral-domain EDI-OCT (Carl Zeiss Meditec, Inc., Dublin, CA, USA), the macular cube and HD 5-line scan mode were selected to image the retina, and the scan line had to be centered on the macular fovea. The mean macular thickness of the center area in Early Treatment Diabetic Retinopathy Study (ETDRS) sectors was provided automatically (Figure 1A). The subfoveal choroidal thickness was measured as the distance between the outer portion of the hyper reflective line corresponding with the RPE to the inner surface of the sclera (Figure 1B) were performed by two examiners. For all OCT findings and measurements, the mean values of measurements from the two independent experienced observers were obtained for further analysis.

Classification and Follow-up of the Patients

After 3 months of observation, spontaneously resolved CSC were diagnosed in the patients with evidence of complete subretinal fluid absorption.

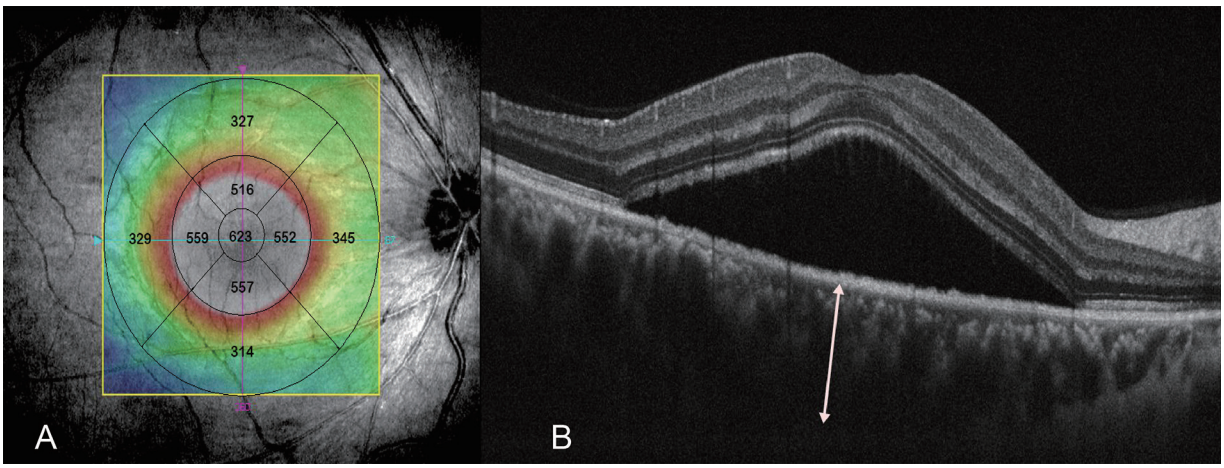

Figure 1. ***A,*** The mean macular thickness of the center area in ETDRS sectors was provided automatically, we analyzed the inner center area. ***B,*** The double-headed arrow represented the subfoveal choroidal thickness.

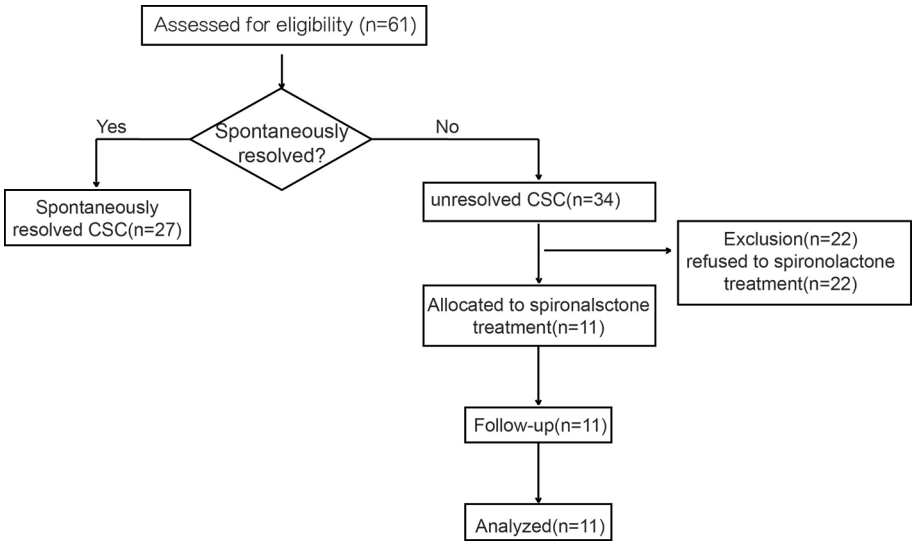

Figure 2. The schematic of the classification and follow-up schedule.

On the contrary, after 3 months of observation, the patients had persistent or increasing SRF existence were defined with unresolved CSC group (Figure 2). The patients were classified into two groups according to follow-up OCT examination.

Spironolactone Treatment and Follow-up Examinations

Among the unresolved CSC patients, 11 patients received the treatment with oral spironolactone 40 mg/day for two months. Follow-up examinations with BCVA and OCT were measured at 1 month and 2 months after the spironolactone treatment. The central macular thickness (CMT in micrometers) was obtained using the macular thickness map. The SFCT (in micrometers) was assessed by manually measuring the distance between the end of the outer segment and the retinal pigment epithelium at the center of foveal. At the end of the 2-month treatment. If the subretinal fluid still existed, the photodynamics therapy (PDT) or laser photocoagulation were treated (Figure 2). The treatment was ceased in the circumstances of hyperkalemia (>5 mmol/l) or hypotension (<90/60 mmHg).

Statistical Analysis

SPSS 19.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. All data were expressed as the mean ± SEM. Snellen BCVA (best corrected visual acuity) was converted to logarithm of the minimum angle of resolution (logMAR) BCVA for analysis. Pearson's *Chi-squared* test was used to compare the gender and hypertension proportions. An independent-samples *t*-test was used to compare the difference of age and refractive error and the SFCT and aldosterone levels in different groups. The Spearman's Rho was used to evaluate the correlation between SFCT and aldosterone level. Variables before and after spironolactone treatment were compared using a pared-samples *t* test. p value ≤ 0.05 were considered significant.

Results

Patient Demographics and Clinical Characteristics

In the present study, 72 eyes from 61 patients, 50 men and 11 women, with a mean age of (43.1 ± 5.9) years were examined. The number of eyes and patients, and the characteristics of the patients (age, gender, refractive error) in each group were summarized in Table I. There was no significant difference in the mean age, gender, refractive error, among the two groups, and the spontaneously resolved CSC ratio was 27/61. Among all patients, 21 had hypertension, and the distribution of hyperpietic were summarized in Table II. The proportion of hyperpietic in unresolved group was significantly higher ($p<0.05$).

Mean SFCT and Aldosterone Level According to CSC Groups

A significant difference was found between the eyes in resolved CSC group (408.6±108.2 μm) and the unresolved CSC group (450.7±62.1

Table I. Demographic and statistical data of the subjects.

	Patients with CSC		
	resolved CSC	unresolved CSC	*p*-value
No. patients	27	34	
No. eyes	29	43	
Age (y)	42.9±6.2	43.3±5.8	0.792
Sex, female:male	7:20	4:30	0.274
Refractive error (D)	-0.29±1.10	-0.09±0.92	0.444

μm). The mean subfoveal choroidal thickness in unresolved CSC eyes was greater than that in resolved CSC eyes (p<0.05, Figure 3A).

We also examined the plasma aldosterone levels in of different CSC groups. Aldosterone levels were in the normal range for all the patients (143.0±53.6 ng/L). In the spontaneously resolved CSC group, the serum aldosterone was (122.5±50.5 ng/dl) and in the unsolved CSC group, it was 159.3±50.9 ng/dl (p<0.05, figure 3B). Among all the patients, the aldosterone level was significantly associated with subfoveal choroidal thickness in both revolved CSC eyes (r=0.316, p<0.05), and unresolved CSC eyes (r=0.307, p<0.05, Figure 4).

Table II. The distribution of hyperpietic.

	Hypertension(+)	Hypertension(-)	
Resolved CSC	6	21	27
Unresolved CSC	16	18	34
	22	39	

The Effectiveness of CSC Treatment with Spironolactone

Twelve eyes of 11 patients were included in the study, characteristics and the examine result of OCT at baseline, 1 month and 2 months after spironolactone treatment are summarized in Table III. Five patients (No. 2, No. 3, No. 9, No. 10, and No. 11) were cured completely, one patient (No. 11) recover completely only 1-month treatment. And in four patients (No. 1, No. 6, No. 7, No. 8), the subretinal fluid decreased but still existed at the end. No. 5 patient had no significant change in CMT at 2 months, No.4 patient aggravated in the second month.

On OCT evaluation, CMT and SFCT decreased significantly from (477.1±110.5 μm, 430.1±86.3 μm) at baseline to (312.2±143.7 μm, 384.9±83.9 μm) at the end of treatment (p<0.05, respectively, Table III and Figure 5). The changes in OCT images of three spironolactone treated patients is shown in figure 6.

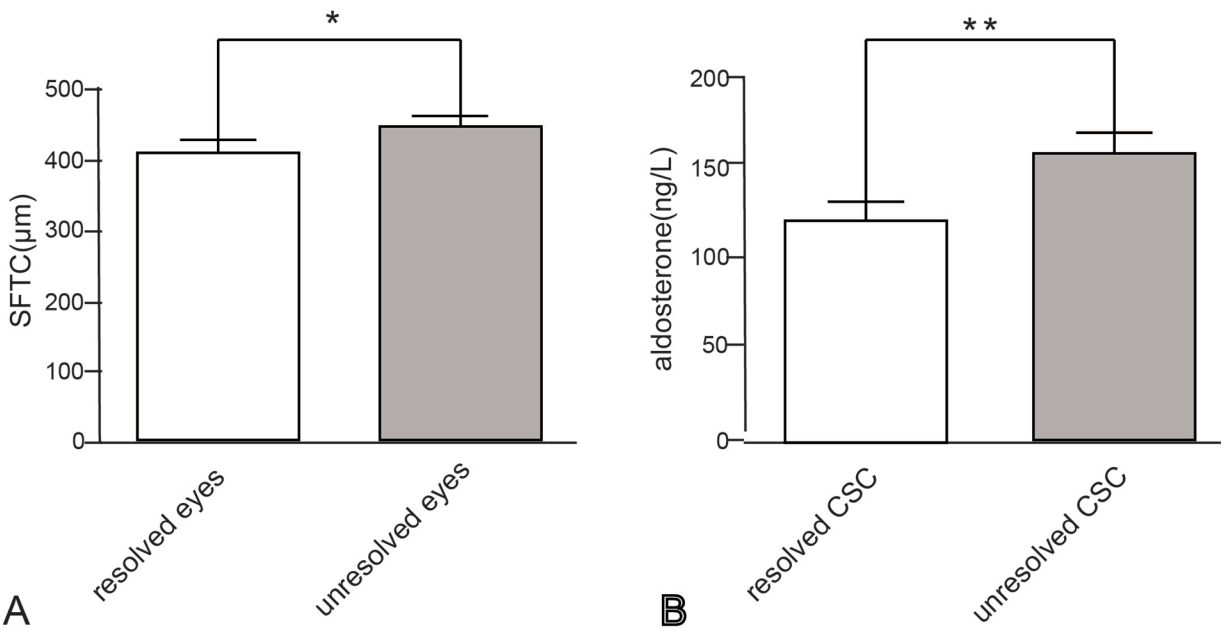

Figure 3. ***A,*** The mean subfoveal choroidal thickness in unresolved CSC eyes was greater than that in resolved CSC eyes. ***B,*** In the unresolved CSC group, the serum aldosterone level was greater than that in the spontaneously resolved CSC group.

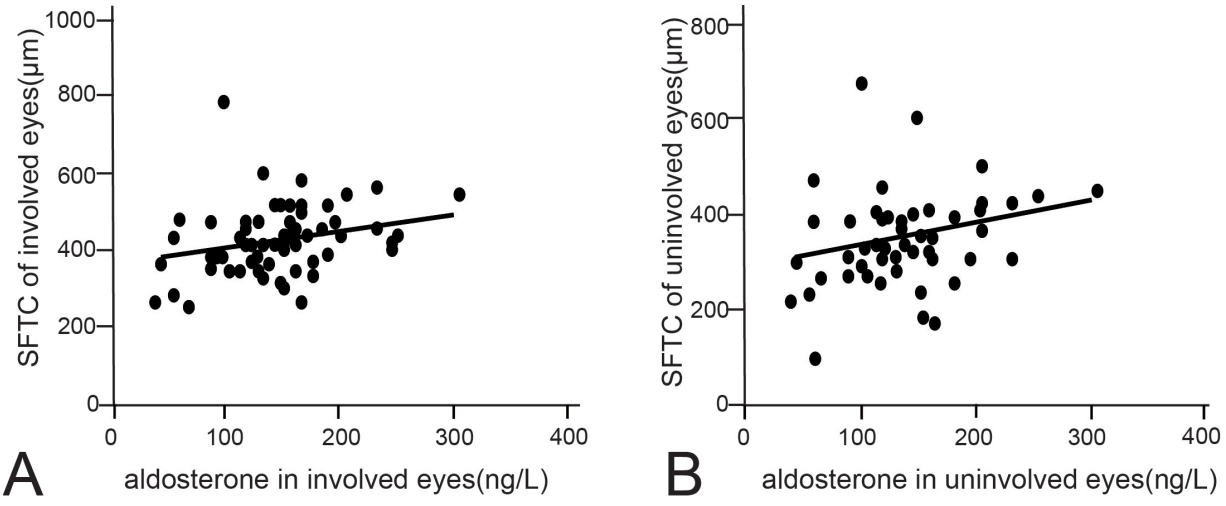

Figure 4. ***A,*** The aldosterone level was significantly associated with subfoveal choroidal thickness in involved CSC eyes. ***B,*** The aldosterone level was significantly associated with subfoveal choroidal thickness in uninvolved CSC eyes.

The BCVA (in logMAR) at baseline, 1 month and 2 months after spironolactone treatment are shown in Table III. The mean BCVA was 0.43 ±0.35 at baseline, 0.16± 0.11 at the end of treatment. The BCVA at end was significantly improved compared with baseline BCVA ($p<0.05$).

Discussion

We grouped the CSC patients into the spontaneous resolved and unresolved groups according to the 3 months follow-up OCT examination[5], self-limiting is a feature of CSC, especially the acute CSC. And the period of spontaneous resolution was 2 to 3 months[16], so we chose the standard of 3 months to minimize the effect of spontaneous regression.

In our study, 22 individuals with hypertension, the proportion of hyperpietic in unresolved group was significant higher, as well as the average level of serum aldosterone. All the serum aldosterone levels are in the normal range. It is produced from the adrenal like the glucocorticoid[12]. Excessive mineralocorticoid and glucocorticoid may cause hypertension[12,13], a risk factor for CSC[14-16]. The

Table III. Demographic and OCT data of the spironolactone treated patients.

Patient Number	Duration of spirolactone Treatment	BCVA (logMar)			CMT (μm)			SFCT (μm)		
		baseline	1 month	2 months	baseline	1 month	2 months	baseline	1 month	2 months
1	2 months	0.30	0.22	0.10	607	284	280	460	379	368
2	2 months	0.22	0.22	0.10	404	276	206	513	445	376
3	2 months	0.10	uncheck	0.10	410	uncheck	204	500	uncheck	484
4	2 month	0.30	0.22	0.30	304	295	308	327	313	337
5	2 months	0.22	0.22	0.22	497	489	549	400	427	408
6	2 months	0.22	0.22	0.10	466	460	435	486	465	465
7	2 months	0.10	0.10	0	347	238	233	426	330	340
8 (od)	2 months	0.52	0.30	0.30	613	561	501	521	530	510
8 (os)		0.52	0.30	0.30	593	538	495	505	450	432
9	2 months	0.6	0.6	0.2	553	298	206	386	286	265
10	2 months	0.6	uncheck	0	360	uncheck	193	402	uncheck	402
11	1 month	1.4	0.2	/	571	136	/	235	232	/

Baseline: The time when the spironolactone treatment began.

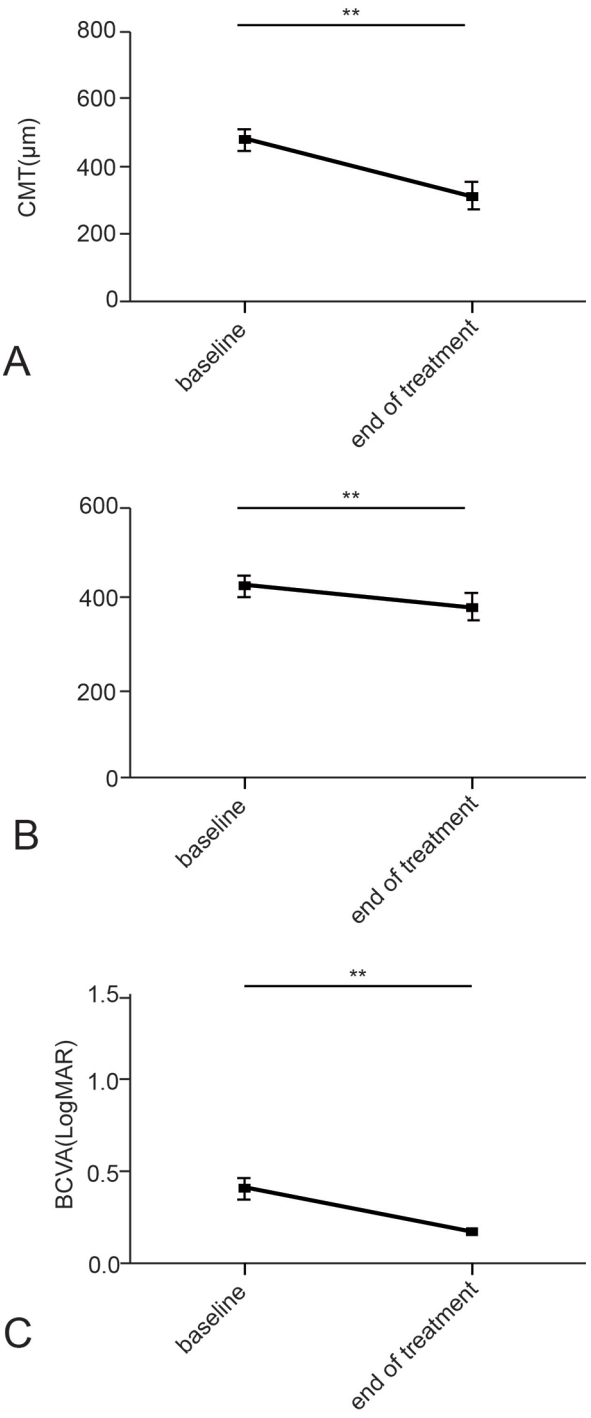

Figure 5. ***A***, On OCT evaluation, CMT decreased significantly after 2 months treatment. ***B,*** On OCT evaluation, SFCT decreased significantly after 2 months treatment. ***C,*** The BCVA at 2 months was significantly improved compared with baseline.

role of glucocorticoid in the pathophysiology of CSC was described in many studies[17-19]; however, no correlation between glucocorticoid levels and duration of disease was found. Zhao et al[11] discovered that mineralocorticoid receptor (MR) is involved in rat and human ocular chorioretinopathy, they hypothesized that CSC might result from excessive signaled of mineralocorticoid receptor by glucocorticoids. High aldosterone/MR signaling may elevate the vascular tone. However, choroid is vascular tissue, high aldosterone/MR signaling also happen in the choroid[20,22]. So, the higher level of serum aldosterone may cause higher blood pressure in the unresolved group. The persistent high serum aldosterone levels may cause the dysfunction of vessel and inhibit the recover of CSC.

At present, the studies of choroidal vessels in CSC patients are controversial. Tittl et al[23] pronounced the subfoveal choroidal blood flow (CBF) was increased significantly in the group of patients with CSC. Doro et al[24] found what they considered to be a non-echogenic band under the RPE in patients with CSC through high-resolution ultrasonography, and using the indocyanine green angiography the bilateral choroidal vascular hyperpermeability was described, which was agreed with the bilateral choroidal thickness increase[8-10]. We also measure the subfoveal choroidal thickness (SFCT) using EDI-OCT[25], the mean subfoveal choroidal thickness was 450.7±62.1 μm in unresolved CSC group and it was greater than resolved CSC group 408.6±108.2 μm (p<0.05), this result indicated the SFCT might be a parameter predict the acute CSC spontaneous resolution possibility. According to many previous studies, SFCT increases in the CSC eyes, and the subfoveal choroidal thickness is thicker in eyes with unilateral CSC than in unaffected fellow eyes, and the unaffected fellow eyes is increased too[6,26]. Those results remind that patients with CSC have choroidal vascular hyperpermeability in both eyes, even if only one eye presented subretinal fluid[27]. And choroidal blood flow is influenced by various systemic factors[28]. The bilaterality changes of the choroidal in CSC supports a hypothetical systemic etiology for the disease.

To the best of our knowledge this is the first report to identify the correlation between the choroidal thickness and aldosterone level. Among all the patients, the aldosterone level was significantly associated with subfoveal choroidal thickness in unresolved CSC eyes (r=0.316, p<0.05), it was significantly associated with subfoveal choroidal thickness in unresolved CSC eyes as well (r=307, p<0.05). The choroidal thickness reflects the choroidal blood flow in a way, which is influenced by various systemic factors such as hypertension. And some learners have shown

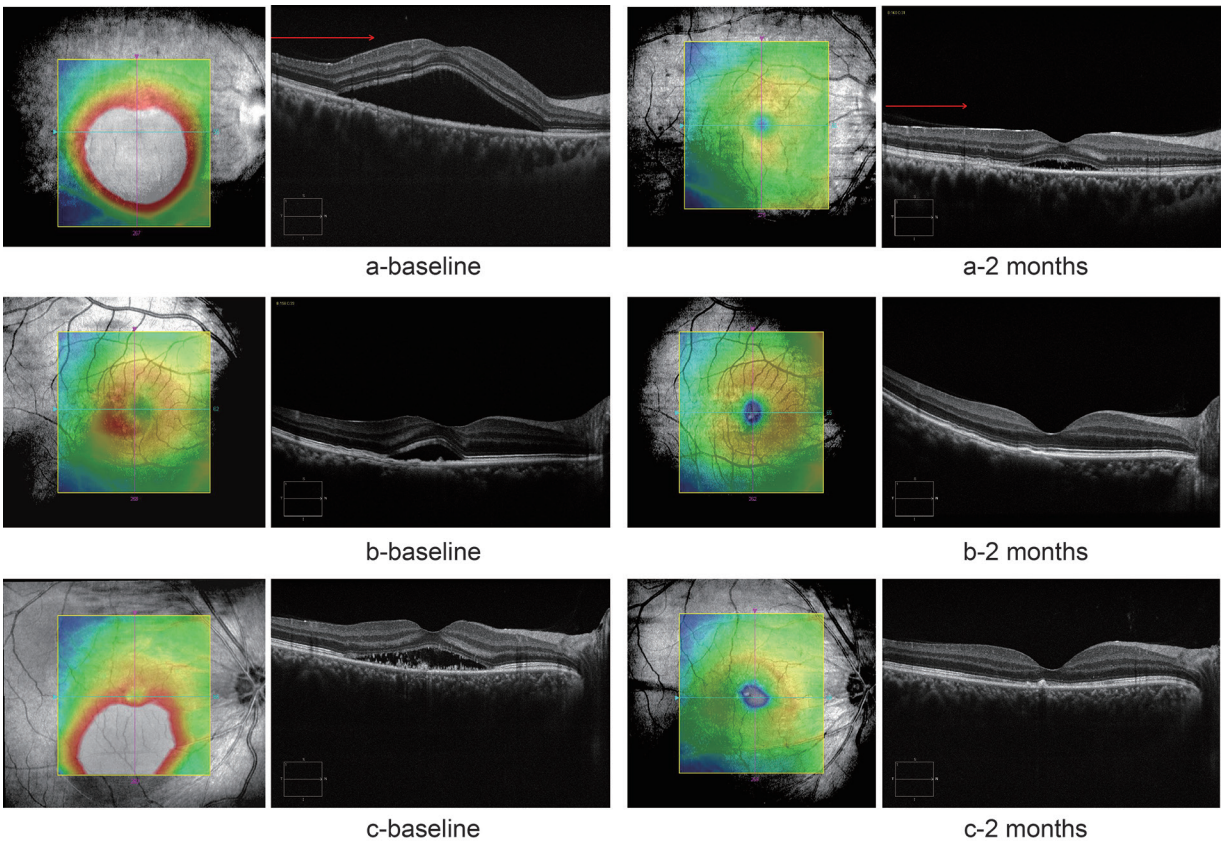

Figure 6. Changes of OCT horizontalscans (red arrows) and macular maps of 3 CSC patients before and after spironolactone treatment.

evidence of hyperdynamic circulation within the choroid in eyes with CSC[23,29]. As stated before, excessive aldosterone may lead to hypertension[21], and increased hydrostatic pressure will lead to pigment epithelium detachment (PED) formation, focal leakage occurs into the subretinal space[30]. In summary, the higher aldosterone level induces the thicker SFCT.

According to Bousquet et al[31] and our result that aldosterone level in unsolved CSC group is higher, we treat 11 from unsolved CSC group with oral spirolactone 20 mg twice daily for two months. Considering the side effect that the serum potassium level increased and blood pressure decreased, the low dose of 40 mg everyday was chosen. In this study, no side effects observed during the treatment. After the treatment, not only the subretinal fluid was absorbed and the central macular thickness was decreased, but also the BCVA was improved or stabled. And the recovery rate was 5/11, improvement rate was 9/11. However, no clear effect was found in one patient (No. 5), and the SRF was persistent. One patient (No. 4) aggravated in the second month. In the end, the photodynamics therapy (PDT) or laser photocoagulation were taken in those four patients and the subretinal fluid absorbed incompletely. So, further studies should be designed to determine the suitable patients and optimal dose.

Conclusions

Our results showed that unresolved CSC patients exhibited significantly higher aldosterone levels. The correlation analysis revealed that SFCT was positively associated with the aldosterone level. And the mineralocorticoid receptor antagonism will improve the CSC. Summarize those results from previous studies, our findings suggest that the aldosterone may be a risk factor to the CSC.

Conflict of interest

The authors declare no conflicts of interest.

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