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ORIGINAL RESEARCH

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Correlative study on retinal microvascular changes and sex hormones in male patients with central serous chorioretinopathy

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Abstract

Central serous chorioretinopathy (CSC) is a disease in which the outer retinal barrier is damaged with high incidence in young adult males. We aimed to analyze the correlations between retinal microvascular changes and sex hormone levels. The vascular density of the superficial retinal capillary plexus (SCP), deep retinal capillary plexus (DCP), foveal avascular zone (FAZ) area, choriocapillary blood flow area, and the subfoveal choroidal thickness (SCT) were investigated by optical coherence tomography angiography (OCTA). We also determined the levels of sex hormones (adrenaline (AD), norepinephrine (NE), dopamine (DA), corticosteroids (Cor), aldosterone (ALD), estradiol (E2) and total testosterone (TT)). The relationship between sex hormone levels and OCTA parameters was then determined. We detected significantly higher levels of NE, Cor and TT in serum from the observation group than in the control group ($p < 0.05$). Significant correlations were identified between SCT and choriocapillary blood flow area in the affected eyes, contralateral eyes and healthy eyes in the control group ($p < 0.05$). SCT levels of both eyes in the observation group were higher and the choriocapillary blood flow area was smaller than in the control group. The SCT in affected eyes from the observation group were higher than the contralateral eyes ($p < 0.05$). The choriocapillary blood flow area was significantly smaller than in the contralateral eyes ($p < 0.05$). Correlation analysis unveiled that NE, Cor and TT levels were positively correlated with SCT in CSC patients and negatively correlated with choriocapillary blood flow area ($p < 0.05$). The serum levels of sex hormone levels in male CSC patients were different from those in healthy men of the same age. Our findings suggest that the serum levels of NE, Cor and TT levels may influence the pathogenesis of CSC by affecting SCT thickness and choriocapillary blood flow.

Keywords

Male; Central serous chorioretinopathy; Optical coherence tomography angiography; Sex hormones; Retinal microvascular changes

1. Introduction

Central serous chorioretinopathy (CSC) is rare in clinical practice and occurs frequently in young adult males. Most patients have a good prognosis, although some patients are prone to the development of chronic CSC which can cause permanent impairment of visual function [1–3]. Once the outer retinal barrier is damaged, the leakage of fluid from the choriocapillaris through retinal pigment epithelium (RPE) lesions results in retinal neuroepithelial detachment in the macular area combined with focal retinal pigment epithelial detachment. Subsequently, patients experience mild visual loss, darkening of vision, hue changes, and a central relative dark area. Medical research suggests that the pathogenesis of CSC is linked to choroidal vascular hyperpermeability, disruption of the RPE barrier, as well as choroidal dysfunction. At present, the specific pathogenesis of CSC remains unclear but may be associated with multiple factors, including ischemia, infection, inflammation, and immune response; however, there is no strong evidence to support these possibilities [4–6]. Due to the differences in CSC pathogenesis between genders, the relationship between sex hormones and CSC has become a significant hotspot in research [7].

Optical coherence tomography angiography (OCTA) is a newly developed technique for fundus examination. In contrast with traditional examinations, this technique does not require the injection of contrast agents; it also has included a wider array of indicators, a better safety profile and can provide quantitative data relating to ocular blood flow [8–10]. In this study, we investigated the relationship between sex hormone levels and OCTA parameters in male CSC patients in attempt to identify factors involved in the pathogenesis of CSC. We

found that the serum levels of sex hormones s in male CSC patients were different from those of healthy men of the same age. In addition, alterations in the serum levels of NE, Cor and TT may participate in the development of CSC by affecting SCT thickness and choriocapillary blood flow. Our findings provide new reference guidelines for clinical research.

2. Subjects and methods

2.1 Study subjects

2.1.1 Sample size assessment

First, we considered the required sample size. According to published data, S = 12.37 and δ = 7.31. The following parameters were established for the current study: α = 0.05 (bilateral) $t_{\alpha/2}$ = 1.96, with a power of 1–β = 0.9, and t_{β} = 1.282. The following formula was used to determine the sample size; this required 60 cases in each group.

$$N1 = N2 = \frac{2S^2(t_{\alpha/2} - t_{\beta})^2}{\sigma^2}$$

2.1.2 Case data

We recruited 60 male patients with CSC patients who were admitted to the hospital as an observation group and 60 males of the same age who passed a health examination without fundus lesions as a control group. The inclusion criteria were as follows: CSC patients who were diagnosed with CSC by fundus photography, optical coherence tomography (OCT), fundus fluorescein angiography (FFA) and other examinations; all with monocular CSC. We also included patients with clinical sudden vision loss, darkening of the vision or hue yellowing, metamorphosis or micropsia and other clinical symptoms. Of the 60 cases, 25 were in the chronic phase and 35 were in the acute phase. The course of disease ranged from 1 day to 6 months, with a mean of 1.12 $\pm$ 0.25 months. For inclusion, patients needed to be aged 20 to 45 years and be able to complete the relevant examinations. The exclusion criteria were as follows: patients with hypertension, diabetes and other systemic diseases; previous ocular trauma and surgery; the use of exogenous sex hormones; glaucoma, maculopathy and other ocular lesions.

2.2 Methods

2.2.1 Detection of serum levels of sex hormones

Blood samples were collected from all subjects from 14:00 PM to 17:00 PM. Prior to blood collection, the subjects were required to sit quietly for half an hour, and 5 mL of whole blood was collected from the forearm vein and placed in a vacuum blood collection tube and centrifuged at 4000 r/min for 15 min. The supernatant was placed in a microcentrifuge tube and stored in a freezer at –20 °C. Epinephrine (AD), norepinephrine (NE), dopamine (DA), cortisol (COR), aldosterone (ALD), estradiol (E2) and total testosterone (TT) levels were measured by radioimmunoassay.

2.2.2 OCTA examination

OCT and OCTA examinations were performed by the same ophthalmologist with the Optovue RTVue-XR Avanti instrument (G1214719, Optoveu Inc., Fremont, CA, USA). We used the 6 mm $\times$ 6 mm OCT imaging mode for retinal blood flow, and each B scan of the OCT data frame consisted of 304 A scans. Each B scan repeated the OCT angiogram at the same position at least twice. Furthermore, OCTA was performed with the Supervisory Control And Data Acquisition (SSADA) algorithm [10] with a working wavelength of 840 nm and 7000 axial scans per second. After scanning the retinal and choroidal vessels, OCTA can be divided into four layers: the superficial and deep retinal plexus, the outer retina and the choriocapillaris. Data relating to the vessel density of the superficial capillary plexus (SCP), deep capillary plexus (DCP), foveal avascular zone (FAZ) area, and choriocapillary blood flow area of the retina, can be acquired directly from built-in software. We also measured the subfoveal choroidal thickness (SCT); the SCT is the vertical distance from the outside of the subfoveal retinal pigment epithelial layer to the inner surface of the sclera.

2.3 Statistical methods

Data were processed by SPSS 19.0 statistical software (Chengdu Enruiqi Information Co., Ltd. Sichuan, China). (Kolmogorov-Smirnov normality test, Levene's test for homogeneity of variances were used, and nonparametric tests were utilized for variables that did not fit a normal distribution). Measurement data are presented as ($\bar{x} \pm s$). The independent sample t-test was used to compare means between the two groups. Pearson's correlation analysis was used for correlation analysis. $p < 0.05$ was statistically significant.

3. Results

3.1 Age comparisons

The age of males in the observation group ranged from 20 to 45 years, with a mean age of 35.45 $\pm$ 10.13 years. The age of males in the control group ranged from 20 to 43 years, with a mean age of 36.17 $\pm$ 10.74 years. There was no significant difference between the two groups in terms of age (t = 0.378, p = 0.706).

3.2 Early hyper-fluorescence and/or leakage of FFA corresponded to changes in OCTA images of the choriocapillaris layer

High blood flow signals were observed in the corresponding areas of fundus fluorescein angiography (FAA) early fluorescence and/or leakage in the affected eyes of CSC patients in OCTA, as shown in Fig. 1.

3.3 Comparison of sex hormone levels between the observation group and control group

The serum levels of NE, Cor and TT in the observation group were significantly higher than those in the control group ($p <$

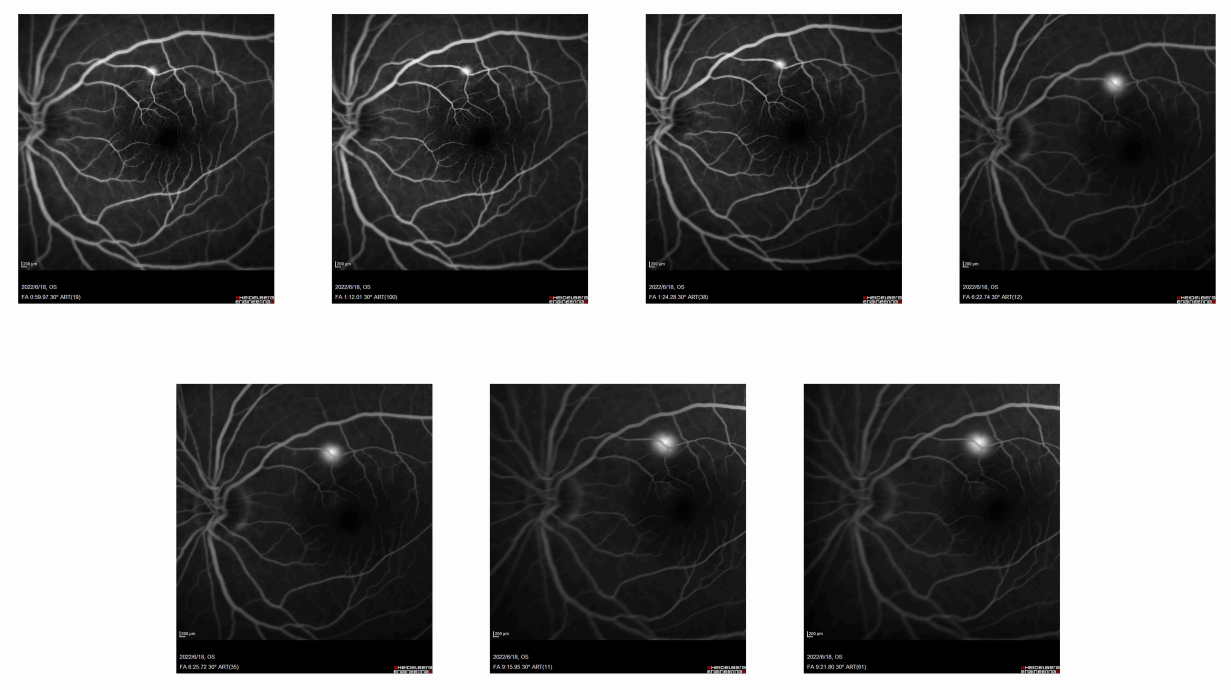

FIGURE 1. High blood flow signals in the corresponding areas of fundus fluorescein angiography (FAA) early fluorescence and/or leakage in OCTA.

0.05) (Table 1).

3.4 Comparison of OCTA parameters between both groups

There were significant relationships between OCTA parameters, SCT and choriocapillary blood flow area between the affected eyes, contralateral eyes, and healthy eyes in the control group ($p < 0.05$). The levels of SCT in both eyes in the observation group were remarkably higher than that in the control group, and the choriocapillary blood flow area was smaller than in the control group. Furthermore, the SCT levels in the affected eyes of patients in the observation group were significantly higher than their contralateral eyes; in addition, the choriocapillary blood flow was significantly lower than that in their contralateral eyes ($p < 0.05$) (Table 2).

3.5 Relationship between sex hormone levels and OCTA parameters in CSC patients

Correlation analysis showed that the serum levels of NE, Cor and TT were positively correlated with SCT levels in CSC patients and negatively correlated with choriocapillary blood flow area ($p < 0.05$) (Table 3).

4. Discussion

CSC is a disease in which the outer retinal barrier is damaged, thus resulting in the leakage of fluid from the choriocapillaris through RPE lesions. Subsequently, this causes retinal neuroepithelial detachment in the macular area combined with focal retinal pigment epithelial detachment. Patients experience several clinical manifestations, including mild visual loss, darkening of vision, hue changes, and central relative dark areas [11–14]. The incidence of CSC differs significantly between genders and occurs predominantly in men and rarely in women. As clinical research advances, our understanding of CSC has developed from the RPE level to the choroidal level. It is now generally accepted that the pathogenesis of CSC is associated with choroidal vascular hyperpermeability, RPE barrier disruption, and choroidal dysfunction [15, 16]. In FFA examinations, we observed RPE barrier disruption and fluorescein leakage. In addition, ICGA examinations revealed choroidal circulation disorder, vasodilatation and leakage. In this study, we found that high blood flow signals were observed in the corresponding areas of FAA early fluorescence and/or leakage in OCTA, thus suggesting that FAA and OCTA examinations can efficiently detect fluorescein leakage, thus validating our hypothesis [17, 18].

OCTA is a new technique used to examine fundus lesions over recent years. This method can clearly demonstrate the morphological characteristics of superficial choroidal vessels and can quantitatively detect retinal blood flow signals [19, 20]. In the present study, OCTA revealed that the SCT of the affected eyes of CSC patients was significantly thicker than that of the healthy eyes. Previous researchers speculated that SCT thickening may be associated with choroidal vasodilatation, choroidal vascular hyperpermeability, and choroidal interstitial edema; in addition, SCT thickening has also been proven to be an important trigger of choroidal structural and functional changes [21–23]. Moreover, this study also identified a reduced choriocapillary blood flow area in CSC patients compared to their healthy eyes, thus indicating that in addition to SCT thickness changes, CSC also involves pathological changes such as choriocapillaris injury and reduced blood flow. Notably, in addition to the affected eye, the contralateral eye of CSC patients also showed changes, including SCT

TABLE 1. Comparison of sex hormone levels between the observation group and the control group (ng/mL).

Group	n	AD	NE	DA	Cor	ALD	TT	E2
Observation group	60	0.85 ± 0.16	9.78 ± 1.29	4.25 ± 1.02	121.25 ± 16.58	0.16 ± 0.02	3.94 ± 0.56	0.02 ± 0.01
Control group	60	0.90 ± 0.17	4.53 ± 1.15	4.37 ± 1.05	107.48 ± 17.11	0.15 ± 0.04	3.21 ± 0.48	0.02 ± 0.01
t		1.659	23.531	0.635	4.477	1.732	7.667	0.000
p		0.100	<0.001	0.527	<0.001	0.086	<0.001	1.000

Note: AD: adrenaline; NE: norepinephrine; DA: dopamine; Cor: corticosteroids; ALD: aldosterone; TT: total testosterone; E2: estradiol.

TABLE 2. Comparison of OCTA parameters between both groups.

Group	n	SCT (μm)	SCP vascular density (%)	DCP vascular density (%)	FAZ area (mm^2)	Choriocapillary blood flow area (mm^2)
Observation group						
Affected eyes	60	473.15 ± 84.48	48.35 ± 7.45	50.14 ± 5.69	0.35 ± 0.05	9.51 ± 1.07
Contralateral eyes	60	356.89 ± 86.54^{a}	48.44 ± 6.59	50.31 ± 6.63	0.34 ± 0.06	9.72 ± 1.12^{a}
Control group	60	248.47 ± 56.98^{ab}	48.74 ± 7.14	50.28 ± 6.11	0.34 ± 0.07	10.97 ± 1.08^{ab}
F		127.153	0.050	0.013	0.545	31.451
p		<0.001	0.951	0.987	0.581	<0.001

Note: Compared with affected eyes in observation group. $^{a}p < 0.05$; compared with the contralateral eyes in observation group, $^{b}p < 0.05$. SCT: subfoveal choroidal thickness; SCP: superficial capillary plexus; DCP: deep capillary plexus; FAZ: foveal avascular zone.

TABLE 3. CSC Relationship between sex hormone levels and OCTA parameters in CSC patients.

Parameters	SCT	SCP vascular density	DCP vascular density	FAZ area	Choriocapillary blood flow area
AD	$r = 0.135$	$r = 0.155$	$r = 0.127$	$r = 0.112$	$r = 0.151$
	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$
NE	$r = 0.341$	$r = 0.174$	$r = 0.115$	$r = 0.089$	$r = -0.311$
	$p < 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p < 0.05$
DA	$r = 0.154$	$r = 0.162$	$r = 0.095$	$r = 0.093$	$r = 0.207$
	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$
Cor	$r = 0.366$	$r = 0.127$	$r = 0.083$	$r = 0.211$	$r = 0.158$
	$p < 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$
ALD	$r = 0.121$	$r = 0.122$	$r = 0.113$	$r = 0.189$	$r = 0.119$
	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$
TT	$r = 0.357$	$r = 0.117$	$r = 0.117$	$r = 0.203$	$r = -0.325$
	$p < 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p < 0.05$
E2	$r = 0.089$	$r = 0.132$	$r = 0.059$	$r = 0.177$	$r = 0.178$
	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$

Note: SCT: Subfoveal choroidal thickness; SCP: superficial capillary plexus; DCP: deep capillary plexus; FAZ: foveal avarzone; AD: adrenaline; NE: norepinephrine; DA: dopamine; Cor: corticosteroids; ALD: aldosterone; TT: total testosterone; E2: estradiol.

thickening and a reduced choriocapillary blood flow area. These data indicate that the pathogenesis of CSC may be correlated with systemic factors.

Previously, researchers have reported that several hormones may play an important role in CSC pathogenesis [24, 25]. In this study, the serum levels of NE, Cor and TT tended to increase in male CSC patients when compared with healthy volunteers of the same age. Mental stress, a strong stress response, and hypertension are all risk factors for CSC. In these physiological states, sympathetic excitability of the human body will increase and secrete substantial amounts of catecholamines, including AD, NE and DA [26]. In this study, the levels of NE and Cor were positively correlated with SCT thickness in the affected eyes of CSC patients. Furthermore, NE was also negatively correlated with choriocapillary blood flow area. Previous research suggested that NE and Cor may lead to the development of CSC by stimulating dopamine receptors in the choroid and enhancing sympathetic nerve activity [27, 28]. Furthermore, RPE cells express androgen receptors. In physiological states, there is a fine balance between male and female hormones. Once this balance is disturbed, the levels of catecholamines and adrenocorticotropic hormone increase due to increasing tissue oxygen supply and the restoration of nitrogen balance, thus promoting dehydrogenase activity in the tricarboxylic acid cycle and the regulation of 2,3 diphosphoglycerate metabolism [29]. In this study, serum TT levels were discovered to be increased in CSC patients and were positively correlated with SCT thickness and negatively correlated with choriocapillary blood flow area in their affected eyes.

However, the results of OCTA examination will be affected by exudation, pigment epithelial detachment, the presence of subretinal fluid and other factors; thus data and images arising from OCTA may be inaccurate. Moreover, the sample size included in this study was small and our analysis only featured a single center; thus, our conclusions may be biased. Therefore, further research, involving larger sample sizes, is now required to fully investigate OCTA.

5. Conclusions

The serum levels of sex hormone in male CSC patients differed from those in healthy men of the same age. In addition, serum levels of NE, Cor and TT may be involved in the development of CSC by affecting SCT thickness and choriocapillary blood flow in patients.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

MLW and YYR—designed the study and carried them out; MLW, YYR, HFZ, JWZ and XBZ—supervised the data collection, analyzed the data, interpreted the data, prepared the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of Hangzhou Lin'an District the First People's Hospital (Approval no. 2020001). Written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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