Central Serous Chorioretinopathy And Selective Serotonin Reuptake Inhibitors

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Abstract

Aim: To investigate the relationship between central serous chorioretinopathy (CSC) and selective serotonin reuptake inhibitor (SSRI) antidepressant drugs.

Methods: The files of patients diagnosed with CSC who applied to our clinics were analyzed retrospectively. Group 1 was formed from patients who had never used any antidepressant drug. Group 2 and Group 3 were composed of patients who did not stop and stopped using SSRI after the third month, respectively. Ophthalmological examinations, optical coherence tomography and fundus fluorescein angiography images of the patients were analyzed and the groups were compared with each other.

Results: Group 1, Group 2 and Group 3 had 122, 8, 12 eyes, respectively. The time for complete resolution of subretinal fluid (SRF) in Group 3 was statistically significantly shorter than Group 1 and Group 2 ($p < 0.01$). In Group 2, the time for complete resolution of SRF was significantly longer than Group 1 ($p < 0.05$).

Conclusion: SSRI group antidepressant drugs might be an important factor in CSC etiology and prognosis. Discontinuation of these drugs may accelerate subretinal fluid resolution.

Background

Selective serotonin reuptake inhibitors (SSRI) are chemical agents that increase serotonergic activity in the synaptic cleft. SSRIs were prescribed more frequently by clinicians day after day due to their relatively low side effect profiles. The lower anticholinergic, antihistamine and cardiotoxic effects of these drugs compared to alternative antidepressants caused them to be preferred more frequently. The most common side effects of SSRIs are gastrointestinal system intolerance and sexual dysfunction. The SSRI group antidepressant drugs used in clinical practice today are fluoxetine, sertraline, citalopram, paroxetine, fluvoxamine, and escitalopram. SSRIs are currently used not only in major depression, but also in the treatment of anxiety, panic disorder and obsessive compulsive disorder and blumia neurosa. Because SSRIs also have anxiolytic, antioxidant and appetite reducing effects (1)

In the literature, SSRI group antidepressant drugs have been associated with some eye pathologies. Depression-associated dry eye disease (2), increased risk of acute closed-angle glaucoma (3), mydriasis-related intraocular pressure decrease in open-angle cases (4), cataract (5, 6), decrease in ganglion cell complex and retinal nerve fiber layer thickness (7), optic neuropathy (8), maculopathy (9, 10) and retinal vein occlusion (11, 12). In this study, we aimed to investigate the possible relationship of SSRI group antidepressant drugs with CSC. According to our literature research, our study is the first controlled and randomized clinical trial in this direction.

Methods

In this multicentric and retrospective clinial study; medical files of the patients who were admitted to our clinics between February 2018 and May 2019 were reviewed. The presence of CSC was diagnosed by fluorescein angiography (FFA) and optical coherence tomography (OCT). All OCT and FFA images were taken with the same machine (Topcon 3D OCT-2000FA, Tokio, Japan) by same technician and evaluated by the same retina specialist (AA).

Patients who did not develop spontaneous healing within the first 3 months were included into this study. Cases with any other choriodal or retinal disorders that may cause exudation in macula, drusen, pathological myopia, intraocular inflammation, retinal vasculopathy, diabetic retinopathy, angioid lines, cataract, corneal pathology, history of uveitis or glaucoma, trauma and hereditary dystrophies were excluded from the study. Patients using antidepressants or psychiatric drugs other than SSRI and with history of preganancy were also excluded. The eyes of the patients who had a second attack within the 9-month follow-up period after the first episode were not included in the study.

Eyes that included into this study were divided into three groups. Group 1 (control group) was formed from patients who had never used any antidepressant drug. Group 2 and Group 3 were composed of patients using the SSRI group antidepressant medication for at least 9 months before the first CSC attack. Patients in Group 2 were made up of people who continued using SSRI at the request of the psychiatrist. Patients in Group 3 were made up of patients who were discontinued using SSRI upon our request and with the permission of psychiatrist. Nine-month follow-up notes, ophthalmologic examinations and imaging findings of the patients were collected. The data obtained were compared with each other. Beginning from the 3rd month, if SRF was resisted, patients in all groups were used 250 mg acetazolamide (Diazomid, Sanofi Aventis, France). Patients in Group 3 were also used 40 mg propranolol hydrochloride (Dideral, Sanofi Aventis, France) on the recommendation of the clinic of psychiatry after the SSRI was discontinued.

The distribution of variables was measured by Kolmogorov Simirnov test. In the analysis of quantitative independent data, Mann-Whitney U test was used. Wilcoxon test was used to analyze dependent quantitative data. Chi-square test was used in the analysis of qualitative

independent data. SPSS 26.0 program was used in the analysis and significance level was set at less than 0.05.

Results

A total of 142 eyes of 134 patients were included in the study. Group 1, group 2 and group 3 had 122, 8, 12 eyes, respectively. All of the patients that had CSC bilaterally were in Group 1. All patients in Group 2 and Group 3 were using 20 mg of fluoxetine (Prozac, Lilly, USA) or 100 mg of sertraline (Lustral, Pfizer, USA) once daily. In Group 2, 6 people were using fluoxetine and 2 was using sertraline. In Group 3, 5 people were using fluoxetine and 7 was using sertraline. Pigment epithelial detachment was present in 79.5% of the patients included in the study, but there was no statistically significant difference between the groups (p 0.05). None of the patients in the study developed any additional eye problems (increased eye pressure, uveitic attacks etc) within the 9-month follow-up period.

The mean age of Group 1, Group 2 and Group 3 was 48.11 ± 5.03, 47.75 ± 6.02 and 46.64 ± 5.89 years. In Group 1, Group 2 and Group 3, the female:male ratio was 37:85, 3:5 and 4:8, respectively. There was no statistically significant difference between the ages and gender distribution of patients in Group 1, Group 2 and Group 3 (p 0.05) (Table 1). The mean time needed for complete resolution of SRF was 206.0 ± 28.9; 253.8 ± 22.4 and 123.7 ± 9.1 days in Group 1, Group 2 and Group 3, respectively. The time for complete resolution of SRF in cases that discontinued SSRI (Group 3) was statistically significantly shorter than cases that never used SSRI (Group 1) and continued SSRI (Group 2) (p 0.01). In the group that continued to use SSRI (Group 2), the time for complete resolution of SRF was significantly shorter than the group that never used SSRI (Group 1) (Table 1).

Table 1
Demographic characteristics of the groups and the time for complete resolution of subretinal fluid

		Grup 1 (never used SSRI)			Group 2 (SSRI continued)			Group 3 (SSRI discontinued)			p	
		Mean ± SD/n-%		Med	Mean ± SD/n-%		Med	Mean ± SD/n-%		Med		
Age (year)		48.11 ± 5.03		48.0	47.75 ± 6.02		47.5	46.64 ± 5.89		48.0	0.998	K
Gender	Male	85	69.7%		5	62.5%		8	66.7%		0.898	X^2
	Female	37	30.3%		3	37.5%		4	33.3%			
SRF resolution time (day)		206.0 ± 28.9		198.5	253.8 ± 22.4		260.5	123.7 ± 9.1		122.5	0.000	K

K Kruskal-wallis (Mann-whitney), X^2 Ki-kare test, W Wilcoxon test, SSRI Selective Serotonin Reuptake Inhibitor, SRF Subretinal fluid, SD Standardized deviation, n number, Med Median, LogMar Logarithm of the Minimum Angle of Resolution

There was no statistically significant difference between the groups in the mean BCVA values at beginning, 3rd month, 6th month and 9th month (p 0.05). In all groups, within the 3rd, 6th and 9th months BCVA improvement (p 0.05). Although not statistically significant, at 3rd month the improvement in BCVA in Group 3 was higher other groups (p 0.692) (Table 2).

Table 2
The best corrected visual acuity changes of the groups

	Grup 1 (never used SSRI)				Group 2 (SSRI continued)				Group 3 (SSRI discontinued)				p	
	Mean ± SD/n-%			Med	Mean ± SD/n-%			Med	Mean ± SD/n-%			Med		
BCVA (LogMar)														
Beginning	0.84	±	0.16	0.8	0.85	±	0.17	0.8	0.85	±	0.16	0.8	0.999	K
3rd month	0.73	±	0.24	0.5	0.76	±	0.26	0.8	0.70	±	0.27	0.5	0.692	K
6th month	0.28	±	0.26	0.2	0.33	±	0.28	0.3	0.25	±	0.22	0.2	0.829	K
9th month	0.08	±	0.10	0.0	0.10	±	0.13	0.0	0.05	±	0.07	0.0	0.721	K
Change from beginning														
3rd month	-0.11	±	0.11	-0.2	-0.09	±	0.09	-0.1	-0.15	±	0.18	-0.2	0.771	K
Intergroup change p	0.000			w	0.046			w	0.000			w		
6th month	-0.56	±	0.27	-0.7	-0.52	±	0.28	-0.5	-0.60	±	0.23	-0.6	0.725	K
Intergroup change p	0.000			w	0.012			w	0.011			w		
9th month	-0.76	±	0.15	-0.7	-0.75	±	0.19	-0.7	-0.79	±	0.15	-0.7	0.705	K
Intergroup change p	0.000			w	0.002			w	0.002			w		

^{K} Kruskal-wallis (Mann-whitney), $^{X^2}$ Ki-kare test, ^{w} Wilcoxon test, BCVA Best corrected visual acuity, SSRI Selective Serotonin Reuptake Inhibitor, SD Standardized deviation, n number, Med Median, LogMar Logarithm of the Minimum Angle of Resolution

Discussion

CSC usually affects young or middle-aged male adults and is usually unilateral (13). In its typical presentation, localized serous detachment of the neurosensory retina containing the macula is observed and spreads to the surrounding retina over time. One or more pigment epithelial detachments may be observed in some of the eyes with CSC. Patients generally complain of metamorphopsy, scotoma in the visual field and blurred vision. Micropsy, dyschromatopsy, or reduced contrast sensitivity may also develop. CSC could also be asymptomatic in rare cases (14).

Choroid and RPE dysfunction; subretinal fluid (SRF) is the most important causes of leakage (15, 16). Vascular hyperpermeability and obstruction belong to pachicoroid vascular changes. Lobular choroidal ischemia and venous obstruction have been shown to be the cause of fluid leakage from the choriocapillaris. Low perfusion and hydrostatic pressure due to subretinal fluid may be the cause of secondary damage on RPE (17). SRF originates from choriocapillaries, so photoreceptors can feed enough to survive despite long-term separation. CSC associated detached retina may induce the release of vascular endothelial growth factor (VEGF) into the subretinal area, and trigger the development of choroidal neovascularization in the eye (18).

Beside OCT and FFA, OCT angiography (OCTA) and indocyanine green (ICG) angiography are helpful in diagnosis of CSC. In typical cases, one or more fluorescent spots appear in FFA, indicating fluid leakage. A fluorescent leak area that expands with a serous separation and late accumulation occurs in 10–15% of cases. The Amsler grid test may be useful in demonstrating metamorphopsy. Hyperopia often develops in the affected eye (19–23). All cases we included in our study had typical CSC findings in both FFA and OCT imaging (Fig. 1).

In CSC, pathology is usually self-limiting and resolved. Visual acuity often turn back to previous level after a few months after the SRF dissolves, but visual problems may sustain after the fluid has dissipated (3). Even most of the cases has only one attack, recurrence may develop in the first year in 30–50% of patients. We did not include the eyes that had a second attack in our study. It has been reported that chronic CSC, called Type II, may develop in 5% of eyes. The time threshold considered to be for chhronic CSC ranges from 3 to 6 months (9, 24). In our study, we did not include the eyes that improved spontaneously before 3 months. From this perspective, it can be said that the eyes in our study were not acute but might be chronic.

Since there is a high possibility of spontaneous recovery in acute cases, follow-up without treatment is generally recommended (25). In chronic CSC management, most ophthalmology clinics recommend treatment (26–30). Intravitreal injection of acetazolamide or finasteride, eplerenone, spironolactone, propranolol, vitamins and non-steroidal anti-inflammatory drugs, photodynamic therapy, anti-VEGF agents, transpupillary thermotherapy and subthreshold lasers are the main treatment options (31–37). Treatment is recommended if resorption does not develop within 3–4 months or the patient has bilateral involvement or acute CSC recurrence and chronic CSC is diagnosed (26, 30). The patients we included in our study were started orally with acetazolamide and propranolol treatment, starting 3 months after the CSC attack developed.

Some of the most important risk factors for CSC development are aggressive personality and physiological stress. CSC often affects freelancers, managers, entrepreneurs and actively working men with a high stress burden. In the literature, CSC; It has been reported in many publications that it is more common in people with type-A or narcissistic personality (38–41). Therefore, it has been reported that psychological intervention, sleep patterns or beta-blocker drug treatments may prevent relapses or progression to chronic CSC (42–44). The patients in this study were followed-up without applying medical treatment and advice stress-reducing recommendations for the first 3 months.

There are publications in the literature indicating that shift work and sleep disorders can be important and independent risk factors for CSC. In these individuals, cortisol and catecholamine changes that develop with disruption of the circadian rhythm may be the triggering element of CSC. Although the relationship between CSC and melatonin level has not been shown yet; there are studies claiming that providing sleep patterns by melatonin may be useful in patients with CSC (45). There are publications claiming that early diagnosis and treatment of obstructive sleep apnea (OSA) may decrease the risk of CSC. Although the prevalence of OSA has been shown to be high in cases with CSC, objective evidence to support OSA screening in these patients is not sufficient today (40, 41). It is also suggested that glucocorticoids, mineralocorticoids and testosterone play a role in the pathogenesis of CSC. There is widespread proof that cortisol has a significant effect on the capillary permeability of the choroid. It has been reported that 5–10% of cases with Cushing's syndrome characterized by high cortisol develop simultaneous CSC (41, 46, 47). None of our cases had a history of OSA or exogenous glucocorticoid use that could be the cause of endogenous steroid elevation.

There are also some publications reporting that CSC may also be associated with catecholamines. In a meta-analysis, the relationship between CSC and catecholamine and drugs that can raise blood pressure was determined. High risk of CSC has been shown with the use of agents that increasing sympathetic activity (pseudoephedrine, amphetamine and oxymetazoline) (41). None of our cases had a history of sympathomimetic drug use.

Most of our cases also were male patients with high stress load. Our suggestions to rearrange the lifestyle may contributed to the high spontaneous improvement that developed especially in the first 6 months. SSRIs are also widely used today as an anxiolytic drug. Discontinuation of these drugs sometimes causes psychiatrists to worry about anxiety in the patient going out of control. This worry was the most important reason why SSRIs were not interrupted in Grup 2. There was no other antidepressant or anxiolytic drug was started in patients in Group 3 whose SSRI was discontinued. The first thing that makes our study special is that it is the article in the literature that reports the association of SSRI and CSC with the most cases. The most important contribution of our study to the literature might be demonstrating the discontinuation of SSRI could accelerate SRF resolution in CSC.

Propranolol is a non-selective adrenergic beta receptor blocker. Since it has a lipophilic molecular structure, its effect on central nervous system and neurons is strong. Propranolol treatment, which was initiated later in stress and anxiety control in patients in SSRI discontinued Group 3, may have contributed positively. Because beta blockers are drugs that inhibit the adrenergic system and cause sedation and anxiolytic effects. Propranolol also strongly blocks β_2 adreno-receptors and causes evidet vasoconstriction. This vasoconstriction may be another reason for propranolol to positively contribute to CSC treatment (1). Because there are studies in the literature that argue that there may be a relationship between vasodilation and CSC. Fraunfelder et al. has been reported the inhibitors of phosphodiesterase type 5 enzym (tadalafil, sildenafil, vardenafil) that used in the treatment of erectile dysfunction might be the etiological cause of CSC. (25). Propranolol treatment was started to all patients in Group 3 on the recommendation of the clinic of psychiatry after the SSRI was discontinued. Therefore, it may be thought that the main reason for the difference between the groups could be due to propranolol.

This study has some limitations. Firstly, small sample size and short follow-up time can be meaningful. Another point to consider is that it is not clear whether the earlier developed SRF resolution in Group 3 was due to discontinuation of the SSRI or the initiation of propranolol.

Conclusions

In conclusion, CSC is a mysterious pathology that is still not fully understood due to its multi-factor etiology, sophisticated pathogenesis and extensive systemic association. It is still unclear whether acute CSC therapy is clinically useful as it resolves spontaneously in its natural

course. In cases lasting more than three months, considering its etiology and pathogenesis, it could be said that the best option for this disease is individualized approach. While the risk factors in etiology are being investigated, questioning the use of antidepressant drugs especially in the SSRI group and discontinuing them in appropriate patients may positively contribute to the etiology and prognosis.

Abbreviations

CSC Central serous chorioretinopathy

SSRI Selective serotonin reuptake inhibitor

FFA Fluorescein angiography

OCT Optical coherence tomography

OCTA Optical coherence tomography angiography

SRF Subretinal fluid

VEGF Vascular endothelial growth factor

ICG Indocyanine green

OSA Obstructive sleep apnea

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committees of the University of Health Sciences (Study number: 17073117-050.99-2789) and was organized and adhered to the tenets of the Helsinki Declaration. Informed consent was obtained from all participants before the study.

Consent for publication

Consent is obtained from the participants, the ethics committee and the clinics where the authors worked to publish the study.

Availability of data and material

The data produced and analyzed during the current study is not publicly available due to the prohibition of hospital's archive system, but could be obtained from the corresponding author upon plausible and acceptable request.

Competing interests

The authors declare that there is no competing interest regarding the study.

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Authors' contributions

Dr.Altun has undertaken important roles in planning the study, performing operations, monitoring and analyzing data. All the other authors made important contributions in the direction of patients and in the statistical analysis process.

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Figures

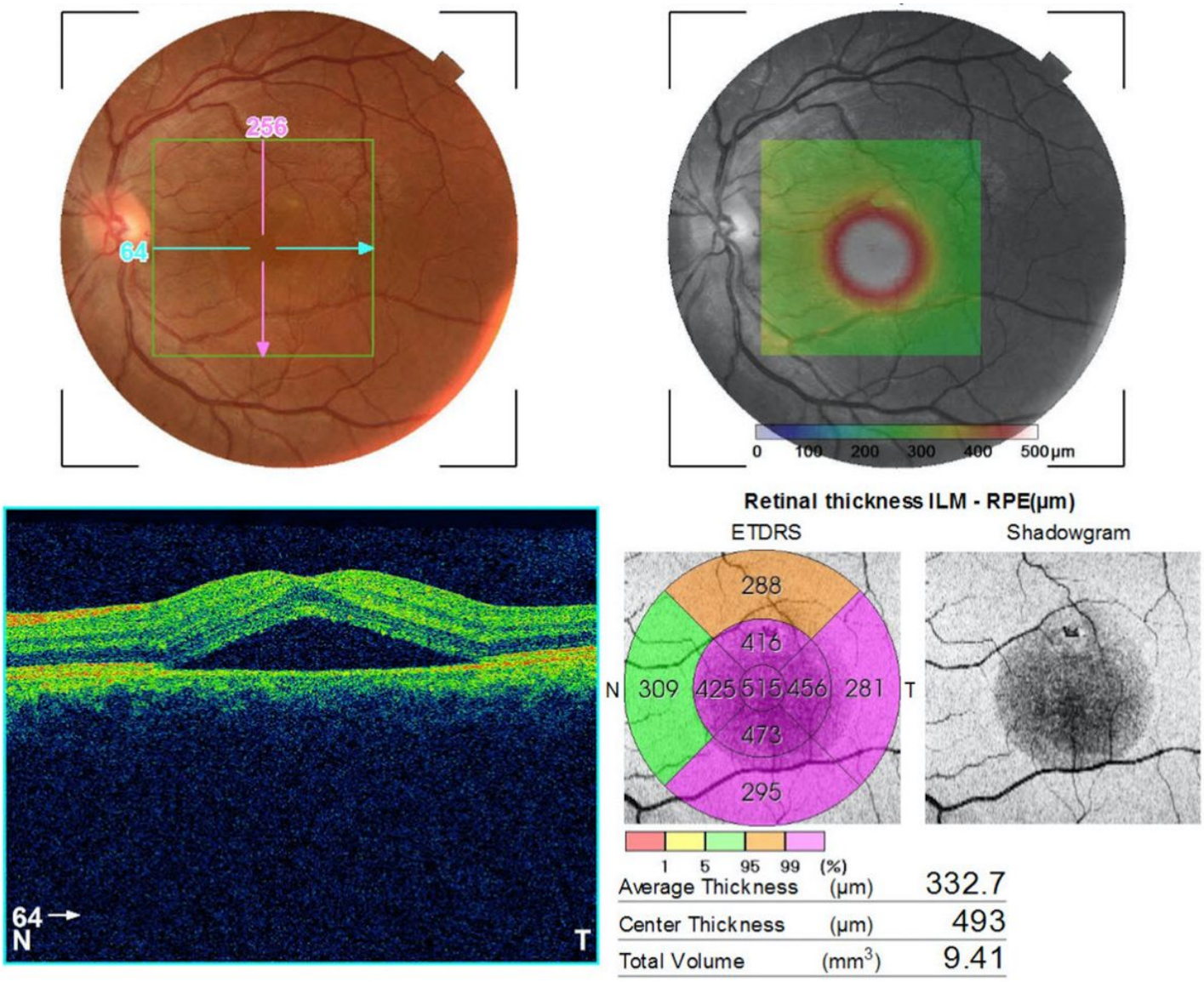

Figure 1

Optical coherence tomography image of a case with central serous chorioretinopathy