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Diagnosed a Patient with Central Serous Chorioretinopathy? Now What?: Management of Central Serous Chorioretinopathy

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Abstract

Purpose of review: *What is the goal of your paper? What questions did you seek to answer?*—The goal of this paper is to provide a comprehensive review of the management options for central serous chorioretinopathy (CSCR).

Recent findings: *Summarize the latest research on your topic*—The majority of cases of acute CSCR may be managed with observation and cessation of corticosteroids, if possible, as well as life-style modifications including stress reduction and control of hypertension. The management of chronic disease is more challenging and may include either medication or laser-based treatment.

Summary: *What answers did you find? What are the major takeaways/conclusions of your examination? What's the impact on future research?*—Management of CSCR necessitates an individualized and selective treatment approach. There is overall poor evidence for the use of systemic and intravitreal medications. From this class of treatments, mineralocorticoid receptor antagonists appear to have the greatest potential. Although conventional thermal photocoagulation may be used in select cases, the most promising treatment options at this time for chronic CSCR are photodynamic therapy, either half-dose or half-fluence, and non-damaging (subthreshold) retinal laser therapy.

Keywords

central serous chorioretinopathy; central serous retinopathy; cscr; csr; photodynamic therapy; subthreshold laser; micropulse; spironolactone

Background

Central serous chorioretinopathy (CSCR) is an idiopathic disorder characterized by serous detachments of the neurosensory retina and alterations of the retinal pigment epithelium

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Compliance with Ethical Guidelines

Conflict of Interest

Raquel Goldhardt declares no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

(RPE).¹ CSCR is a major cause of decreased vision among middle-aged male individuals. Other symptoms include metamorphopsia, micropsia, reduced contrast sensitivity and scotoma. Patients with this condition may also be asymptomatic if the serous detachments and leakage are extramacular in location. The incidence has been cited to be 5.8 per 100,000 people,² and most often, individuals have concurrent usage of corticosteroids and classically fit the demographic of young or middle-aged men with emotional stress or Type A personalities.³⁻⁶ Additional risk factors include: pregnancy, smoking, untreated hypertension, multisystem autoimmune disease, and obstructive sleep apnea.^{3,7} There is evidence suggesting a slight increased incidence of CSCR in Asian populations as compared to Caucasian populations and disease that is more likely bilateral and multifocal.^{8,9} CSCR has also been suggested to present more aggressively in Black populations.¹⁰ Imaging utilizing optical coherence tomography (OCT) frequently demonstrates changes in both eyes that result from choroidal hyperpermeability, with findings that include subretinal fluid (SRF), irregular RPE, pigment epithelial detachments (PEDs), and a thickened choroid that may be best visualized using enhanced depth imaging (EDI).^{11,12} Fundus autofluorescence (FAF) as well as fluorescence angiography (FA) and indocyanine green angiography (ICG) can also be useful in establishing a diagnosis, assessing for choroidal neovascularization (CNV), and management of the disease. The preponderance of CSCR cases are self-limiting, spontaneously resolving within several months with good visual recovery.¹³ If a single episode converts to multiple recurrences or if there is persistent SRF accumulation, RPE cells begin to decompensate and may lead to widespread RPE atrophy and photoreceptor damage in the affected area and can result in poor vision.^{14,15} In older populations, the diagnosis of CSCR is more challenging because of clinical similarities with the macular degeneration process and possible secondary CNV development; drusen are not a common clinical finding in cases of CSCR. No consensus exists regarding when acute CSCR becomes chronic CSCR, but the chronic term is used once there is persistent SRF with extended RPE changes.

Initial Management

Management of CSCR is typically guided by the individual's needs and natural history. Initial treatment is generally conservative in nature. In patients without prior episode, the classic teaching has been to wait 4 or 6 months for spontaneous resolution before attempting laser photocoagulation.¹ Prompt treatment with photocoagulation has not been demonstrated to improve final vision outcome or the rate of recurrence and carries inherent risks including CNV.^{13,16} In addition to observation, it is imperative to counsel to patients on the importance of corticosteroid cessation, stress reduction, and management of any underlying known risk factors such as untreated hypertension or sleep apnea, as these measures have been demonstrated to have a beneficial effect on resolution of fluid as well as vision.¹⁷

Management of Chronic Disease

Although the management of choice for acute CSCR is typically observation with cessation of corticosteroids and stress reduction, management of chronic CSCR is more challenging, as there is poor evidence for the preponderance of treatment options. Treatment choices for chronic CSCR can be divided into two general categories: medication and laser-based

treatment. Medications may further be subdivided into systemic and intravitreal, while laser-based treatments may be subdivided into photodynamic therapy (PDT), thermal photocoagulation, and subthreshold or nondamaging retinal laser therapy (NRT).

A. Systemic Medications: *Is there good evidence that they work?*

A myriad of systemic medications have been trialed. As a whole, these have had poor evidence, including: rifampin,¹⁸ *Helicobacter Pylori* treatment,^{19–21} carbonic anhydrase inhibitors^{22,23}, finasteride²⁴, beta-blockers,²⁵ antioxidants,^{26–28} aspirin.²⁹ Mineralocorticoid receptor antagonists appear to be the most promising of the systemic medications used in the management of CSCR.

The mineralocorticoid pathway appears to have an impact on choroidal vasculature in animal models, affecting vasodilation, leakage, and choroidal thickness.³⁰ This is further supported by the association of CSCR with increased levels of endogenous and exogenous corticosteroids.^{3,4,31} The mineralocorticoid receptor antagonists, spironolactone and eplerenone, more commonly used in the treatment of congestive heart failure and primary hyperaldosteronism, have been explored for the management of this condition.^{30,32,33}

Bousquet et al reported the results of their prospective randomized placebo-controlled crossover study, in which chronic CSCR patients receiving spironolactone 50mg daily for 30 days showed significant reduction in SRF and choroidal thickness.³⁴ However, this did not statistically impact visual acuity (VA), which the authors attributed to the small sample size of 16 patients and high baseline VA of approximately 20/34 in the study. Pichi et al. performed a larger prospective randomized placebo-controlled study consisting of 60 patients with chronic CSCR, consisting of three groups that were titrated to spironolactone 50mg, eplerenone 50mg, or placebo for a month, after which they were switched to a different one of these treatments for a month.³⁵ The authors concluded that both spironolactone and eplerenone could be considered equally effective in reducing SRF, while spironolactone may be considered superior to eplerenone in improving VA. Spironolactone is known to have a higher mineralocorticoid receptor affinity as compared to eplerenone, albeit with less specificity, and also has a higher incidence of side-effects including hyperkalemia, gynecomastia, reduced libido, and menstrual changes.³⁶

B. Intravitreal Medications: *Are they indicated?*

Intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents have poor evidence in the management of CSCR,^{37–41} except for in cases where secondary CNV is present. On average, only 4.4 anti-VEGF injections were required over a period of 1.5 years to secondary CNV,⁴² in contrast to approximately 13 injections required over a 2 year period for treatment of neovascular age-related macular degeneration.⁴³

C. Photodynamic Therapy: *how effective is it?*

Laser-based treatments of CSCR are the most promising of the treatments available and can be divided into two groups: photodynamic therapy (PDT) and laser photocoagulation. PDT is proposed to work through vascular remodeling of the choroid and leads to decreased choroidal volume, permeability, and leakage of fluid.^{44,45} Full-dose PDT involves the intravenous administration of the photosensitizing agent verteporfin at a dose of 6mg/m²

body surface area with subsequent activation of the area of interest with a 689nm laser with the fluence of 50J/cm², intensity of 600mW/cm², and treatment duration of 83 seconds.⁴⁶ In attempt to improve the safety profile of the treatment, half-dose verteporfin (3.0 mg/m²) or half-fluence laser (25J/cm²) may be used with similar visual outcomes.^{47–49}

In the Macula Society's large retrospect case series of 237 patients, the clinical response to PDT treatment was not affected by fluence settings, type of leakage seen on FA, corticosteroid exposure, or fluid location (SRF vs. PED).⁵⁰ Additionally, SRF resolved in 81% of eyes, with improvement in vision seen as early 6 weeks from time of treatment. Visual gain was associated with worse initial VA (2 line improvement in 26% and 59% of eyes with VA 20/32 and 20/100, respectively). Treatment with PDT has also decreased the rate of recurrence to less than 10%,^{49,51} as compared to 30–50% if left untreated.^{14,15,52} Further, PDT was found to be an equally efficacious modality of treatment in both corticosteroid and non-corticosteroid related cases of CSCR, and the continuation of corticosteroids at the time of PDT does not preclude a favorable treatment response.⁵³ Figure 1 demonstrates the improvement of SRF that may be seen after PDT treatment.

D. Subthreshold or Non-damaging Retinal Laser Therapy: *does it work?*

Conventional laser photocoagulation may be considered in cases of well-defined extrafoveal leakage to hasten both SRF resolution and vision improvement. However, tissue is permanently damaged in the process and the burn may lead to scotoma, CNV formation, and enlarge over time.¹ In contrast, non-damaging retinal laser therapy (NRT), also called subthreshold laser, does not create collateral tissue damage. This promising new technology raises the temperature of the RPE to just below the protein-denaturation-threshold, which limits transmission of thermal energy to the neurosensory retina, not allowing a visible burn to form. It is hypothesized to improve RPE function through the upregulation of heat shock proteins.⁵⁴ Two types of laser system technologies have been utilized to accomplish NRT: micropulse and modified continuous. Micropulse laser technology works by chopping the emitted continuous laser wave into microsecond pulses energy, and may be utilized on a 810nm diode laser (Iridex Corp, Mountain View, CA), 532nm green, or 577nm yellow laser system (Ellex, Adelaide, Australia; Quantel Medical, Clermont-Ferrand, France; Lightmed USA, San Clemente CA). Duty cycle is typically set to between 5–15%, setting the “on” time of the each 2ms period to 0.15–0.30ms. These 2ms periods are repeated for the duration of the burst exposure, typically between 100 and 300ms. In contrast, the modified continuous laser system uses an algorithm called Endpoint Management (EpM) (Topcon Medical Laser Systems, Santa Clara, CA). This system has the treating physician find the power and duration needed to create a barely visible burn, after which the system modifies the selected values using an Arrhenius-based algorithm to deliver treatment using the 577 nm PASCAL laser without tissue damage.⁵⁴ The most recent studies utilizing NRT are summarized in Table 1. Advantages of NRT include the ability to apply treatment near the fovea as well as the ability to retreat. Given its excellent safety profile, NRT may be a reasonable treatment option in some cases of acute CSCR.⁵⁵

NRT has received increased attention in the most recent years, with the most recent studies summarized in Table 1. NRT utilizing an subthreshold 810nm diode micropulse laser (SDM)

was compared with sham control in a prospective, randomized, double-masked manner by Roisman et al.⁵⁶ After three months, the 10 patients with chronic CSCR who received SDM had statistically significant VA gains of 12.5 letters, as compared to the 5 patients in the sham group that did not. All patients had a trend of improved central macular thickness (CMT) in this study. Lavinsky et al utilized the 577nm PASCAL laser with EpM to deliver NRT in a prospective, nonrandomized, interventional case series of 16 patients with chronic CSCR, finding that it improved VA and SRF.⁵⁷ Treatment was repeated at month 3 in those patients with unresolved SRF. SRF was resolved after a single treatment in 37% of patients, while 75% of patient had resolution of SRF by month 6. Patients gained an average of 12 ETDRS letters within 2 months of treatment, which remained stable over the course of 6 months.

When compared to PDT, NRT was found to be effective in the treatment of chronic CSCR. Ozmert et al performed a retrospective comparative case series of 30 patients with chronic CSCR treated with either half-fluence PDT or 577 nm yellow micropulse NRT.⁵⁸ After 12 months, CMT decreased in both groups (−149.3μm, NRT; −85.9μm, PDT) as did SRF (80.0%, NRT; 72.2% with complete resolution, PDT), while VA had a trend of improvement (+4.2, NRT; + 3.7 ETDRS letters, PDT). Scholz et al also performed a retrospective comparative study with 577 nm yellow micropulse NRT, comparing it against half-dose PDT in 100 patients with chronic CSCR.⁵⁹ Six weeks after treatment, both groups had a statistically significant decrease in CMT (−148μm, NRT; −76μm, PDT) with 36% of eyes in the NRT group showing complete resolution of fluid as compared to 21% in the PDT group. Kretz et al performed a prospective randomized control study that compared SDM with half-dose PDT and observational control among 62 chronic CSCR patients.⁶⁰ This study allowed for retreatment for non-resolving FA and OCT leakage at the 8 week time point as well as at the end of the study at 16 weeks. At 8 weeks, 50% of the NRT group required retreatment as compared to 8% of the PDT group, while at 16 weeks, 30% of the NRT group and 17% of the PDT group were retreated. At the conclusion of the 16-week study, both NRT and PDT (60% vs. 66.7% with no persistent leakage, respectively) demonstrated less leakage on FA as compared to control (37.5%). Change in CMT on OCT was similar in all groups (−69.7 μm, NRT; −109.8 μm, PDT; 89μm, control). VA and contrast VA improved significant in treatment groups (+6.7, NRT; +8.5, PDT; +1.5 ETDRS letters, control), however the PDT group demonstrated a greater increase in contrast VA. Notably, no secondary RPE alterations were detected by FAF after any intervention. Breukink et al is conducting a longer, 8 month, prospective randomized controlled study called the “PLACE trial” comparing PDT to SDM in 156 patients.⁶¹ Estimated to be completed in June 2017, this study’s primary outcome will be absence of SRF on OCT and secondary outcome will be VA, microperimetry, and the National Eye Institute Visual Function Questionnaire (NEI VFQ-25).

When performing NRT, Chen et al found in a prospective, noncomparative, interventional case series of 25 patients that SDM was most effective in eyes with point source leakage.⁶² Luttrull observed that when using SDM, applying a higher number of laser spots within a larger treatment area of treatment may be associated with improved results.⁶³ NRT may also be used for persistent SRF after repeated PDT, although further improvement of fluid is typically not as great as after initial PDT treatment.^{64,65}

Conclusion

Management of CSCR is challenging, particularly in chronic cases. It is important to address this disease in a comprehensive manner, including the assessment of systemic risk factors such as concurrent steroid usage and untreated hypertension. This is particularly important since the available treatments including medication and laser are not always effective.

In order to gain insight into the practice pattern of retina specialists worldwide, Mehta et al distributed an online questionnaire to physicians who had published on CSCR within the prior 2 years.⁶⁶ Of the 107 respondents (82% response rate), 51% were from Asia, 24% were from the United States, and 22% were from Europe. Seventy-nine percent of ophthalmologists offer observation for at least 3 months in cases of acute CSCR, while 46% of ophthalmologists observe for at least 1 month in recurrent cases. For the management of chronic CSCR, 67% of physicians offer PDT, with half-fluence being preferred over half-dose, as their initial treatment option. While there was no consensus among the 35% of physicians that use micropulse laser as to the settings, the majority use a 5% duty cycle with 50% threshold power and pulse duration of 200ms. In regards to medications, 44% of physicians have used eplerenone and 12% have used spironolactone.

There is poor evidence for the majority of the treatments for CSCR. The large spectrum of disease phenotypes in CSCR necessitates an individualized and selective treatment approach. In the preponderance of cases of acute CSCR, we recommend observation with cessation of corticosteroids, if possible, as well as life-style modifications to reduce stress. For chronic or recurrent CSCR, which most define as having symptoms persist for more than 3–6 months, a myriad of treatment options have been studied. There is overall poor evidence for the use of systemic and intravitreal medications, with mineralocorticoid receptor antagonists (i.e. spironolactone and eplerenone) appearing to have the greatest potential from this class of treatments. While conventional thermal photocoagulation may be used in select cases, the most promising treatment options at this time for chronic CSCR are PDT, either half-dose or half-fluence, and NRT.

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Figure 1. Improvement of SRF in the left eye of a patient with chronic CSCR is observed when comparing the OCT before treatment (A) to 1 month after treatment with PDT (B).

Table 1
Overview of Recent Non-damaging (subthreshold) Retinal Laser Therapy (NRT) Studies in Chronic CSCR

Study Authors	Study Design	Laser	Vision Outcomes	OCT Outcomes	Number of Treatments	Duration of Follow-up
Abd Elhamid (2015) ⁶⁷	<ul style="list-style-type: none">■ Prospective■ Interventional case series	<ul style="list-style-type: none">■ Micropulse■ 577 nm	<ul style="list-style-type: none">■ VA: 0.67→0.85■ Contrast Sensitivity (Pelli-Robson): 1.48→1.73	<ul style="list-style-type: none">■ CMT:390→264µm■ SRF:136→10µm	1.26(1–2)	6 months
Kim et al (2015) ⁶⁸	<ul style="list-style-type: none">■ Retrospective■ Interventional case series	<ul style="list-style-type: none">■ Micropulse■ 577 nm	<ul style="list-style-type: none">■ VA (logMAR): 0.21→0.055(3mo)→0.035(final)	<ul style="list-style-type: none">■ CMT 349→251(3mo)→261µm(final)■ Choroidal Thickness: 399→401(3mo)→400µm (final)	2.1 (1–5)	8 months (ave) (range 3–18)
Kretz et al. (2015) ⁶⁹	<ul style="list-style-type: none">■ Prospective■ Randomized, double-masked■ NRT vs half-dose PDT vs sham laser	<ul style="list-style-type: none">■ Micropulse■ 810 nm (diode)	<ul style="list-style-type: none">■ VA (ETDRS letters):<ul style="list-style-type: none">○ NRT:87→93(8wks)→97○ PDT:83→87 (8wks)→91○ Sham:96→96 (8wks) →98■ Contrast VA (Central Vision Analyser): M1 Michelson contrast<ul style="list-style-type: none">○ NRT:0.57→0.60○ PDT:0.41→0.61○ Sham:0.77→0.94	<ul style="list-style-type: none">■ CMT:<ul style="list-style-type: none">○ NRT:274→181(8wks)→204µm○ PDT:330→206(8wks)→220µm○ Sham:326→274(8wks)→237µm	MRT:1.8(1–3) PDT:1.25(1–2)	16 weeks
Malik et al (2015) ⁶⁹	<ul style="list-style-type: none">■ Retrospective■ Interventional case series	<ul style="list-style-type: none">■ Micropulse■ 810 nm (diode)	<ul style="list-style-type: none">■ VA (ETDRS letters): 39.2→45.5	<ul style="list-style-type: none">■ Maximum macular thickness: 414→316.2 µm	1.1 (1–2)	2–12 months
Scholz et al (2015) ⁶⁴	<ul style="list-style-type: none">■ Retrospective case series	<ul style="list-style-type: none">■ Micropulse■ 577 nm	<ul style="list-style-type: none">■ VA (logMAR):<ul style="list-style-type: none">○ 0.36→0.33 (6wks)→0.24 (final)	<ul style="list-style-type: none">■ CMT: 402→309 (6 wks)→287 µm (final)■ Percent Eyes with Resolved SRF:<ul style="list-style-type: none">○ 13% (6 weeks)→24% (final)	1.7 (1–3)	5 months (ave)
Yadav et al (2015) ⁷⁰	<ul style="list-style-type: none">■ Retrospective■ Interventional case series	<ul style="list-style-type: none">■ Micropulse■ 577 nm	<ul style="list-style-type: none">■ VA: 20/40→250/30■ Microperimetry: 75% with improved thresholds	<ul style="list-style-type: none">■ SRF: 232→49 µm	1	8 weeks (ave) (range 4–19)
Breukink et al (2016) ⁵³	<ul style="list-style-type: none">■ Prospective■ Interventional case series■ NRT after PDTx2	<ul style="list-style-type: none">■ Micropulse■ 810 nm(diode)	<ul style="list-style-type: none">■ VA (logMar): −0.04 (change from s/p PDTx2 to after NRT)	<ul style="list-style-type: none">■ Change from s/p PDTx2 to after NRT<ul style="list-style-type: none">○ SRF:−10.1 µm (10% with complete resolution)○ CMT: +4.5 µm	1	39 weeks (range 1–126)

Study Authors	Study Design	Laser	Vision Outcomes	OCT Outcomes	Number of Treatments	Duration of Follow-up
				O Choroidal Thickness: −12.6 μm		
Lavinsky et al. (2016) ⁵⁴	<ul style="list-style-type: none">■ Prospective■ Nonrandomized■ Interventional case series	<ul style="list-style-type: none">■ PASCAL EpM■ 577nm	<ul style="list-style-type: none">■ VA (ETDRS letters gained from baseline): O +12.2 (2 months)→+12.5 (12 months)	<ul style="list-style-type: none">■ CMT: 362→283 μm■ SRF: resolved in 81% of patients■ Choroidal Thickness: 349→293μm	2.2(1–4)	12 months
Ozmert et al. (2016)58	<ul style="list-style-type: none">■ Retrospective■ Comparative case series■ NRT vs. half-fluence PDT	<ul style="list-style-type: none">■ Micropulse■ 577 nm	<ul style="list-style-type: none">■ VA (ETDRS letters) ONRT:67.3→71.5 OPDT:60.7→64.4	<ul style="list-style-type: none">■ CMT ONRT:287→138 μm OPDT:243→157μm■ SRF ONRT:130→13μm (80% with complete resolution) OPDT:117→31μm (72% with complete resolution)	NRT:1.1 (1–2) PDT: 1.1(1–2)	12 months
Scholz et al (2016) ⁵⁹	<ul style="list-style-type: none">■ Retrospective■ Comparative case series■ NRT vs. half-dose PDT	<ul style="list-style-type: none">■ Micropulse■ 577 nm	<ul style="list-style-type: none">■ VA (logMAR) ONRT:0.39→0.31 OPDT:0.35→0.31	<ul style="list-style-type: none">■ CMT ONRT:445→297 μm OPDT:398→322 μm■ SRF ONRT: 36% with complete resolution OPDT: 21% with complete resolution	NRT: 1.4(1–2) PDT: 1.4(1–2)	6 or 12 weeks