Central serous chorioretinopathy (CSCR)

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Von Graefe first coined the term 'central recurrent retinitis' in 1866 for recurrent serous macular detachment. In 1967, Gass explained the pathogenesis and clinical features and named it central serous choroidopathy (CSC). CSCR typically affects middle-aged men and is characterized by serous neurosensory detachment (NSD) of retina at the posterior pole. Most cases are idiopathic and regress spontaneously within 4 months with good visual recovery. However, a few suffer from persistent or recurrent serous macular detachment leading to progressive visual loss. Advances in indocyanine green angiography (ICGA) and optical coherence tomography (OCT) have led to greater understanding of CSCR. Modifications of photodynamic therapy (PDT) have changed CSCR management. Newer treatments in the form of anti-vascular endothelial growth factor (anti-VEGF) and mineralocorticoid receptor (MR) antagonists appear to be promising, but needs more scientific evidence before incorporating them into regular clinical practice.

Definition
CSCR is a disease characterized by localized NSD with or without focal pigment epithelial detachments (PEDs) and altered retinal pigment epithelium (RPE). There are two forms, i.e. acute and chronic. The acute form usually resolves within 4 months, leaving mostly color discrimination defects in few patients. The chronic form is characterized by widespread tracks of RPE atrophy, showing reduced fundus autofluorescence (FAF). Chronic form of the disease can also have irregular RPE detachments and long-standing intraretinal cystoid cavities.

Pathogenesis
The pathophysiology of CSCR is thought to involve multiple etiologies and mechanisms that lead to widespread choroidal circulatory abnormalities and subsequent RPE disturbances. The hyperpermeability of choroid can be caused due to stasis, ischemia or inflammation, which is evident with the staining of the inner choroid in mid-phase ICGA. These hyperpermeable choroidal vessels, hypothesized to cause increased tissue hydrostatic pressure, overcome the barrier function of the RPE and lead to the formation of PEDs. Further increase in hydrostatic pressure in the choroid causes breach in the RPE and allows entry of fluid in the subretinal space. Recently, aldosterone/MR pathway has been postulated in the pathogenesis of CSCR where intravitreal aldosterone had provoked vasodilation, thickening and leakage of choroidal vessels with accumulation of subretinal fluid (SRF) in pre-clinical animal models.

Risk factors
Type-A personality, anti-psychotic medication and psychological stress are independent risk factors for CSCR and depression is associated with increased risk of recurrence. Hypertension, obstructive sleep apnea and patients under systemic and local corticosteroid therapy are at higher risk of developing CSCR. It has been described after the administration of inhalational, intranasal, topical and periocular steroids. Steroid-induced CSCR is an idiosyncratic response with less male predilection with more bilaterality. CSCR has also been reported following kidney, bone marrow and heart transplantations. Diseases, producing increased endogenous cortisol, such as Cushing’s disease and pregnancy, especially the third trimester, increase the risk of having CSCR. Aqueous sample in patients with CSCR showed lower level of platelet-derived growth factor (PDGF), implicating PDGF in the pathogenesis of CSCR. Gastroesophageal reflux and Helicobacter pylori infection have been separately reported to be associated with CSCR and treatment of the above conditions had shown to hasten the rate of SRF resolution. Though the use of phosphodiesterase-5 inhibitors (sildenafil, tadalafil) had shown to cause CSCR, their discontinuation gives conflicting evidence regarding resolution of the disease in different studies. So far, cases of familial CSCR had been reported in the literature, but no clear transmission pattern or genotype has been found to be associated with the disease.

Clinical features
CSCR has become the most common vision-threatening disease after age-related macular degeneration (AMD), diabetic retinopathy and retinal vein occlusion. Men are mostly affected and a recent epidemiological data confer a higher mean age of affected patients, ranging between 39 and 51 years. The older patients show more bilateral, female prevalence and increased risk of developing choroidal neovascularization (CNV). The incidence of CSCR has been noted to be more among Asians and Caucasians, but the disease behaves more aggressively among African-Americans.
In acute presentation, patients usually complain of blurred vision, relative central scotoma, metamorphopsia, dyschromatopsia, hypermetropization and micropsia due to the SRF in the macular area (Figure 1). The hallmark of acute CSCR is a well-demarcated round- or oval-shaped area of NSD over the posterior pole with or without associated serous PEDs. In those patients, loss of foveal reflex provides a good hint toward diagnosis. Phagocytosed photoreceptor outer segments from the outer retina can sometimes appear as tiny yellow dots at the inner surface of RPE23 (Figure 2). SRF in acute CSCR is usually transparent, but occasionally can become turbid due to subretinal fibrin deposition (Figure 3). This fibrin sometimes gets organized to cause subretinal fibrosis, leading to permanent drop in vision. Patients with CSCR can also present with inferior bullous exudative retinal detachment.24 In chronic cases, there are areas of RPE changes and typical RPE atrophic tract in the inferior fundus due to the gravitational effect of long-standing SRF.25 They can also present with chronic CME and secondary CNV.

**Differential diagnosis**

**Age-related macular degeneration**
CSCR, CNV and PCV can be put together in a spectrum of ‘pachychoroid’ condition.26 AMD is the most important differential diagnosis in CSCR patients aged 50 years or more. Secondary CNV, mostly type 2, can develop in patients with chronic CSCR during follow-up or after laser photocoagulation.

**Polypoidal choroidal vasculopathy**
Because of SRD, RPE alteration and choroidal hypermeability in ICG, sometimes it becomes difficult to distinguish PCV from chronic CSCR. The points, which favor the diagnosis of polyps, are subretinal hemorrhage, branching vascular network and leaking polyps in ICGA. OCT typically shows serosanguineous, notched or tall peaked PED and higher optical density of SRF.27

**Optic disc PIT**
Optic disc pits are focal excavations located in the temporal aspect of optic nerve head, creates a communication between the vitreous cavity, the subretinal space and to some extent the subarachnoid space. They produce chronic or recurrent SRD following schisis of inner retina in around half of the cases with variable intraretinal cystoid edema. Careful peripapillary examination and absence of leakage in FA remain diagnostic of optic disc pits.

**Inflammatory diseases**
Vogt–Koyanagi–Harada (VKH), a bilateral granulomatous panuveitic condition, often presents with multiple SRD mimicking CSCR. Apart from its systemic, neurological and dermatological signs, the presence of vitritis, increased choroidal thickening in ultrasound and pinpoint multifocal leaks on FA readily distinguish it from CSCR. Differentiation for this condition is of utmost importance as unlike CSCR systemic steroids are the mainstay of treatment here.

**Autoimmune and vascular disorders**
Autoimmune diseases, such as systemic lupus erythematosus, polyarteritis nodosa and scleroderma, due to the disease processor during systemic steroid therapy can have NSD, complicating the outcome. Non-autoimmune conditions such as malignant hypertension, toxemia of pregnancy and disseminated intravascular coagulopathy can
also present with a secondary NSD due to choroidal arterial occlusion.

**Intraocular tumors**

Various types of choroidal tumors including choroidal hemangioma, choroidal melanoma, choroidal osteoma and choroidal metastasis can cause exudative SRD mimicking CSCR. It is important to differentiate a malignant and potentially lethal condition from CSCR. Ultrasonography is useful in detecting and differentiating the nature of the tumor. In hemangiomas, ICGA shows classical ‘wash-out’ phenomenon in late phases of angiography and EDI-OCT shows increased caliber of large choroidal vessels in the tumor along with normal choriocapillaris.

**Ancillary testing**

**Optical coherence tomography**

SD-OCT and recently enhanced-depth imaging and swept-source technologies have made the understanding of CSCR better by allowing better full-depth visualization of the neurosensory retina, RPE, choroid and choroidal vessels. Elongation of photoreceptor outer segments in the area of a macular SRD is a frequent OCT finding in CSCR. Erosion of photoreceptor outer segments at the site of leakage points toward a mechanical abrasion from an active flow through the RPE break. In active CSCR cases, a combination of SD-OCT with FA identified an RPE elevation or a PED at the leakage sites in most of the cases (Figure 4). Localization of PEDs in the areas of dilated, large choroidal vessels and thickened choroid on SD-OCT with vascular hyperpermeability on ICGA suggest the role of choroidal flow deregulation in the pathogenesis of PED.

In chronic CSR, there can be a hyper-reflective content over Bruch membrane, creating a ‘double layer sign’ in OCT. The thinning of outer nuclear layer, cystoid macular degeneration (CMD) and disruption of the ellipsoid zone in OCT are associated with poorer visual outcome.

**Fundus autofluorescence**

FAF mostly originates from the RPE lipofuscin and reflects RPE health. Focal areas of hypoautofluorescence corresponding to the leakage points in acute CSCR support the hypothesis of a focal RPE defect (Figure 5). The SRD in acute CSCR also shows hypoautofluorescence due to masking effect of SRF and as the disease progresses to become persistent or chronic, there is increasing hyperautofluorescence due to the accumulation of non-shed fluorophores. The pattern of this change in FAF has been shown to correlate with visual acuity. FAF can be pathognomonic in chronic CSCR by multiple hypoautofluorescent ‘gravitational tracks’ with thin border of surrounding hyperautofluorescence (Figure 6).

**Fluorescein angiography**

In acute CSCR, classically there are two leakage patterns in fluorescein angiography (FA). First one,
Figure 4. This 45-year-old male presented with a right eye relative scotoma for 3 weeks. (a) Clinical examination showed subretinal fluid (SRF) together with a pigment epithelium detachment (PED) in the macula. Optical coherence tomography (OCT) shows PED with SRF. FA shows initial pooling of dye in the PED followed by leakage; (b) Left eye shows PED in fundus photo and OCT, with pooling of dye in FA.

Figure 5. This 38-year-old man was treated with ill-defined laser for submacular fluid before he presented to us with active pinpoint leak in FA of the left eye. Fundus autofluorescence (FAF) showed increased autofluorescence suggestive of long standing subretinal fluid with point hypoautofluorescence (black arrow) corresponding with the leak in FA.

Figure 6. Left eye of a post renal transplant patient on long-term systemic steroids showing multifocal pinpoint leaks in CSCR. Note the hypoautofluorescence patches (white arrow) with surrounding hyperautofluorescence (black arrow) suggestive of chronic disease.
the leakage starts as a pinpoint in early phase and then concentrically enlarges in the late phase to appear like an inkblot (Figure 7). Secondly, the leak increases from a pinpoint gradually to ascend and expand like a mushroom cloud or umbrella in the late phase to cause a smoke stack, which is seen in 10–15% of patients (Figure 8). It is caused by an increased protein concentration in the SRF. Chronic CSCR shows diffuse RPE window defect and patchy hyperfluorescence due to RPE atrophy. FA is also useful in differentiating CSC from other diagnoses, such as CNV and VKH, and helps in diagnosing unnoticed extramacular leak in affected or fellow eye.

**Indocyanine green angiography**

ICGA helps to demonstrate the choroidal vascular changes, which contributes in the disease process and can act as a guide to treatment with PDT. ICGA in CSCR shows delay in choroidal filling in the early phase with hypofluorescent areas resulting from non-perfusion of choriocapillaris. This leads to choroidal venous dilatation and choroidal hyperpermeability with the zone of hyperfluorescence in the mid-phase (Figure 9). In the late phase, there is either washout or persistent hyperfluorescence.

**Multifocal electroretinography**

Multifocal electroretinography (mfERG) can indicate more widespread retinal dysfunction in CSCR than appreciated on clinical examination. First-order kernel mfERG amplitudes are reduced in the center and the second-order responses predominantly gets reduced for the peripheral retina.34

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**Figure 7.** Ink blot leak: the hyperfluorescence starts as a pinpoint and then enlarges circumferentially to produce intense hyperfluorescence in late phase similar to the appearance of drop of ink into a piece of paper.

**Figure 8.** Smoke stack appearance: the hyperfluorescent spot starts as a pinpoint and then diffuses upward and laterally to give a mushroom cloud or umbrella-like appearance.
Natural history
Most acute CSCR patients show spontaneous visual recovery within 4 months. However, some progresses to chronic or recurrent disease, which lead to areas of RPE atrophy and pigmentation in the macular area with subsequent visual loss. Up to 50% patients of CSCR develop recurrence within the first year of presentation. A small proportion of patients develop irreversible visual loss due to gross RPE atrophy, subretinal fibrosis, CNV or CMD. Adaptive optics have shown reduced cone density in eyes with resolved CSCR with 20/20 visual acuity compared with controls. This explains the reason for having residual symptoms such as metamorphopsia, scotoma, reduced contrast and color sensitivity even in well-recovered patients after acute CSCR.

Treatment
Observation with or without removal of risk factors
Acute CSCR is a self-limiting disease, with re-attachment of the NSD occurring within 4 months in most cases. Because of this favorable natural history, observation has been considered as an appropriate first-line approach. As high levels of endogenous or exogenous corticosteroids have been implicated in the etiology of CSCR, discontinuation of steroid in any form is advocated. In CSCR, recurrences occur in ~20–50% of patients by 1 year and chronic NSD often leads to permanent loss of visual functions. Lifestyle modification, treatment of sleep apnea and psychosocial therapies has also helped in treating patients prone to have CSCR. So, though observation is the standard initial management in most cases of CSCR, active treatment should be initiated when symptoms persist for more than 3 months. Treatment most of the time speeds up visual recovery, but no treatment could maximize the final visual gain. Early treatment is recommended in cases where rapid recovery of vision is required for vocational reasons, and also where untreated CSCR had previously resulted in a poor visual outcome in the fellow eye.

Argon laser photocoagulation and micropulsed diode laser
Laser photocoagulation, when applied to the RPE leakage points, causes direct thermal sealing effect on the focal RPE defects and favors stimulation of surrounding RPE cells. This hastens the resolution of NSD, but rarely alters the final visual outcome and rate of recurrences. This may be because zonal hyperperfusion and hyperpermeability of the choriocapillaris, the presumptive pathophysiology in CSCR, are not amenable to laser therapy. This treatment method can have adverse effects.
such as permanent scotoma, enlargement of RPE scar, secondary laser-induced CNV, and, rarely, inadvertent foveal burn.\textsuperscript{40} Thermal laser photoagulation is now indicated in the management of CSCR with discrete, solitary or multiple extrafoveal leaking points with persistent NSDs (Figure 10). Subfoveal or juxtafoveal leak and bullous exudative RD are better managed by safety-enhanced PDT rather than argon laser.

There has been a revival of interest in using micropulse diode laser, instead of the conventional argon laser photocoagulation, to treat CSCR. The 810 nm micropulsed diode emissions enable sub-threshold therapy to the RPE and choroid without a visible burn, reducing the risk of structural and functional retinal damage. In a series of 30 patients, the diode group had faster visual recovery and better final contrast sensitivity than the argon laser group without any persistent scotoma.\textsuperscript{41} Nevertheless, the efficacy and safety of micropulse diode laser in chronic CSCR is not proved and randomized controlled trials (RCT) are necessary to fully substantiate the treatment efficacy.

**Photodynamic therapy**

There are reports showing favorable visual outcomes of ICG-guided PDT to treat CSCR.\textsuperscript{42} The analyzed mechanism of action of PDT causing narrowing of choriocapillaris, choroidal hypoperfusion and choroidal vascular remodeling supports its treatment in CSCR, which is primarily a pachychoroid disorder and success of PDT also depends upon the degree of hypermeability on ICGA\textsuperscript{43} (Figure 11). The potential hazards of conventional PDT in AMD, i.e. RPE atrophy, choriocapillaris ischemia, and secondary CNV has made clinicians modify PDT to get the safest form to reduce iatrogenic risks.\textsuperscript{44}

**Conventional PDT**

In nAMD following standard PDT, there is normalization in calibers of the congested choroidal vasculature with a decrease in the extravascular leakage in few pilot studies.\textsuperscript{45} In a recent meta-analysis all the 10 studies that met a standard STROBE criteria showed significant improvement in BCVA after conventional PDT treatment in CSCR.\textsuperscript{46} However, the possible post-treatment visual loss and potential choroidal ischemia have restricted clinicians from the widespread application of standard dose PDT in CSCR patients.\textsuperscript{47}

**Safety-enhanced PDT with reduced verteporfin dosage**

To reduce the potential iatrogenic hazards of PDT, lot of studies in CSCR have tried to modify the dosage of verteporfin or reduce the fluence of laser to minimize its side-effects.\textsuperscript{48} The aim of these studies was to lower the risk of retinochoroidal complications of PDT without compromising its ability to remodel the vascular bed.\textsuperscript{49} In one study, verteporfin at a dose of 3 mg/m\textsuperscript{2}, instead of 6 mg/m\textsuperscript{2} showed a complete resolution of the fluid in 79.5\% and 94.9\% of the half-dose PDT-treated eyes at 1 and 12 months, respectively. Another study reporting the long-term results of half-dose PDT in chronic CSCR showed a dry macula at 12 months for all 27 eyes.\textsuperscript{51} Eyes without PED, duration of CSCR for <6 months

![Figure 10. Resolved subretinal fibrin and subretinal fluid in long standing CSCR following focal laser to extrafoveal leak.](image)
and age younger than 45 years were having better visual improvement. Though studies have tried lower doses of verteporfin, it is the 3 mg group, which had the best results in terms of BCVA and CFT reduction at 6-month follow-up period.50,51

The role and limitations of PDT in CSCR should be emphasized clearly to the patients, as most of them will have good visual potential and there has been sporadic observations of transient impairment of multifocal ERG and development of juxtafoveal CNV with half-dose PDT.52

Safety-enhanced PDT with reduced laser fluence
There are reports of improved efficacy and safety profiles of low fluence PDT in the management of chronic CSCR. The RCT by Bae at al compared half-fluence PDT with intravitreal ranibizumab to treat 16 eyes of chronic CSCR patients and found complete resolution of SRF at 6 months in 79% of the half-fluence group compared with 25% in the ranibizumab group.53 The PDT group also showed significant CFT reduction at the end of 9 months. In other two studies, half-fluence group had better BCVA compared with the standard group at the end of 12 months.54,55

A recent retrospective study with 56 patients of chronic CSCR treated with half-dose and half-fluence PDT divided in equal numbers showed a complete resolution of SRF in 19 (61.3%) and 26 (83.9%) half-fluence-treated eyes at 1 and 12 months. The corresponding values were 25 (86.2%) and 29 (100%) in the half-dose-treated eyes without any statistical difference in BCVA in between the groups with overall 15 and 5 recurrences in the groups, respectively.56 The meta-analysis by Erikitola et al. also concluded that 100% of the studies in reduced fluence group and 42.9% studies of half dose group had recurrence within 1-year-follow-up period.57 So, there can be a cost-effective, superior role of half-dose PDT compared with half-fluence in keeping the macula dry for longer period.

Anti-vascular growth factor injections
Although CSCR is not associated with increased anti-vascular growth factor (VEGF) aqueous or plasma levels, anti-VEGF therapy was proposed in CSCR to reduce the choroidal hyperpermeability.58 A limited number of interventional case series had reported beneficial effects of bevacizumab and aflibercept in terms of visual acuity improvement and SRF reduction without significant complications.59,60 Out of 2 RCTs, the first one showed no difference in terms of visual acuity gain, central
foveal thickness reduction or duration of SRD between bevacizumab and control groups. The second study, by Arevalo et al., showed superior effect of half-fluence PDT to ranibizumab. In a recent meta-analysis, there was no significant improvement with intravitreal bevacizumab, compared with observation, PDT or laser photocoagulation in terms of final visual acuity and central macular thickness.

Transpupillary thermotherapy
Transpupillary thermotherapy (TTT) is a long-pulse, low-energy, 810-nm near infrared laser, which causes choroidal vascular thrombosis. There are studies in which TTT had proved to be safe in focal juxtafoveal leakage instead of thermal laser. Wei and colleagues were the first to report complete resolution of SRF 4 weeks after TTT in a case of chronic CSC with no observed visual improvement. In a large, non-randomized, prospective cohort study, with unmatched control of 15 eyes, 96% of the 25 TTT-treated experienced complete resolution of NSD and leakage on FA at 3 months. Vision improved significantly in 92% of cases compared with 33% in the control group. Still, well-controlled, properly matched RCTs are warranted to find the precise role and efficacy of TTT in the management of CSC.

Anticorticosteroid therapy
Patients with CSC commonly have endogenous hypercortisolism, resulting in trials of medications targeting cortisol pathways. There are anecdotal reports with ketoconazole, mifepristone (RU486), finasteride, rifampin in the treatment of CSC without any long-term acceptable benefit. MR activation in choroid vessels had been shown to be involved in the pathogenesis of CSC. In a recent study, 17 eyes of 13 patients with chronic CSC had improvement of Log MAR visual acuity from 0.42 at baseline to 0.29 and decreased CFT from 339.5 microns to 270 microns at 6 months when treated with 25 and 50 mg of oral efelone per day. Though these studies throw a lot of hope for medical management of CSC, there is a need for extensive research with longer follow-up before they can be accepted in primary oral therapy of CSC.

Conclusion
The pathophysiology of CSCR remains multifactorial. The role of choroidal vascular hyperpermeability related to the deranged mineralocorticoid pathway sounds appealing, but needs more scientific support. Though the natural history of CSC has been thought to be favorable, frequent reports of significant anatomical and functional loss even from a mild course of the disease and the risk of frequent recurrences require early effective treatment. Newer imaging techniques and treatment options have opened new horizons in the management of the disease. In the treatment ‘Safety-enhanced’ PDT using lower doses, oral corticosteroid antagonists, intravitreal anti-VEGF therapy and micropulsed diode laser do merit further research.

References


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