Case Study

Central Serous Chorioretinopathy (CSCR)

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Abstract

Central serous chorioretinopathy (CSCR) is a disease in which a serous detachment of the neurosensory retina occurs over an area of leakage from the choriocapillaris through the retinal pigment epithelium (RPE). It is a self-limited macular disease marked by distortion, blurry vision, and metamorphopsia. Other causes for RPE leaks, such as choroidal neovascularization, inflammation, or tumors, should be ruled out to make the diagnosis. Choroidal neovascularization is also an uncommon complication of CSCR. CSCR most commonly occurs in males and is associated with psychosocial factors such as stress and type A personality and with corticosteroid exposure. It has a high rate of recurrence.

Treatment consists of observation, focal laser, reduced fluence photodynamic therapy, and mineralocorticoid antagonists. ***(1)***

Introduction

Central serous chorioretinopathy (CSC) was first identified and described in 1866 by von Graefe, who referred to the disease as “recurrent central retinitis”. It is a common ocular disease characterized by decompensation of the retinal pigment epithelium (RPE), which results in neurosensory retinal detachment, serous pigment epithelium detachment (PED), and RPE atrophy. It is usually unilateral and predominantly affects young or middle-aged (25 to 50 years) adults, with men being affected more frequently than women. **(**2**)**

In its typical presentation, CSC appears as a localized serous detachment of the neurosensory retina involving the region of the macula without subretinal blood or lipid exudates. The margins of the serous detachment are sloping and merge gradually into the normally attached retina of the posterior pole. Occasionally, it is associated with a single or multiple serous PED.

Patients affected by CSC often complain of blurred vision (usually only in one eye), typically perceived as a dark spot or scotoma in the central visual field, with associated image distortion (metamorphopsia). Other common symptoms include micropsia (reduction of the apparent size of objects), mild dyschromatopsia (abnormal color perception), and reduced contrast sensitivity. However, CSC may also be asymptomatic. **(**3**)**

The visual acuity of people affected by CSC varies widely; Amsler grid testing reveals distortion of the straight lines, which may appear blurred due to a central scotoma. A small relative defect of the afferent pupillary reflex is also occasionally present.

Pathophysiology

Previous hypotheses for the pathophysiology have included abnormal ion transport across the RPE and focal choroidal vasculopathy. The advent of indocyanine green (ICG) angiography has highlighted the importance of the choroidal circulation to the pathogenesis of CSCR. ICG angiography has demonstrated both multifocal choroidal hyperpermeability and hyperfluorescent areas suggestive of focal choroidal vascular compromise. Some investigators believe that initial choroidal vascular compromise subsequently leads to secondary dysfunction of the overlying RPE. **(**4,5**).**
Studies using multifocal electroretinography have demonstrated bilateral diffuse retinal dysfunction even when CSCR was active only in one eye. **(**6**)** These studies support the belief of diffuse systemic effect on the choroidal vasculature.

Personality trait and stress

Type A personalities, systemic hypertension, and obstructive sleep apnea may be associated with CSCR. The pathogenesis here is thought to be elevated circulating cortisol and epinephrine, which affect the autoregulation of the choroidal circulation. Furthermore, Tewari et al demonstrated that patients with CSCR showed impaired autonomic response with significantly decreased parasympathetic activity and significantly increased sympathetic activity. **(**7**)**

Glucocorticoid use

Many reports have suggested that high blood levels of glucocorticoids (also called glucocorticosteroids, corticosteroids, or steroids), mineralocorticoids, and occasionally testosterone are involved in the pathogenesis of CSC. There is extensive evidence of an important effect of the cortisol hormone on the capillary permeability of the choroid, which may contribute to the underlying pathogenesis of CSC. Clinical studies on patients with Cushing syndrome, which is characterized by abnormally high levels of cortisol, found concurrent CSC in 5–10% of cases. The increased risk of CSC during pregnancy is also likely driven by increased levels of endogenous corticosteroids, as ocular dysfunction usually appears during the third semester, but generally resolves spontaneously after delivery. Furthermore, abnormal cortisol elevation may explain the association between CSC and erectile dysfunction, which has been recently suggested by the authors of a large case-control study. **(**8**)**

Endogenous cortisol levels are usually higher in patients with CSC **(**9**)** and the rate of urinary cortisol excretion is increased. **(**10**)** Exogenous systemic corticosteroids (e.g., cortisone) are commonly used to treat inflammation and allergies, but nasal corticosteroid sprays, eye drops, and topical creams can also trigger CSC, aggravate it, and cause relapses. Above all, inhalant/nasal, oral, and injectable steroids seemed to be significant risk factors. **(**11**)** Steroid-induced CSC has less male predilection than idiopathic CSC and frequently has a bilateral presentation. Among solid organ transplant patients receiving long-term corticosteroids, those with renal transplants appear to be at a higher risk, possibly due to underlying renal disease, hypertension, microangiopathy, and previous exposure to hemodialysis, all of which may modify choroidal hemodynamics.

The strong association between steroid use and CSC may be identified by the RPE and choriocapillaris receptor reactivity during systemic corticosteroid treatment. Daruich et al **(**12**)** proposed that excessive activation of the mineralocorticoid receptor (MR) in the choroidal endothelial cells, either by aldosterone or glucocorticoids with a high affinity for the MRs, induces upregulation of the vasodilator potassium channel KCa2.3 that modulates smooth muscle relaxation in the choroidal vessels. Systemic treatment with corticosteroids may damage the posterior blood-retinal barrier, altering the permeability of the choriocapillaris and RPE, resulting in focal areas of increased permeability that lead to subretinal fluid accumulation. **(**13**)** In contrast, mineralocorticoid antagonists reverse the upregulation of KCa2.3 channels in the choroid; this finding supports the use of MR antagonists in CSC treatment. **(**14**)**

Other factors

Infection with Helicobacter (H.) pylori may be a predisposing factor for CSC. It appears that the presence of these bacteria is correlated with the visual prognosis and severity of the clinical manifestations of the disease. Though the mechanism is still poorly understood, infection with H. pylori allegedly creates an increased susceptibility of the retinal tissue to oxidative stress generated by the inflammation.

Patients suffering from kidney diseases, such as membranoproliferative glomerulonephritis type II, may develop retinal abnormalities similar to CSC; this is likely caused by choroidal deposits of the same material that originally damaged the glomerular basement membrane in the kidneys.
Genetic risk factors may also play a role in CSC, possibly via the complement system; however, only very rare familial cases have been reported thus far. **(**15**)** Chronic CSC is associated with genetic variants in ARMS2 and CFH, indicating a genetic overlap between CSC and AMD, otherwise, alleles in ARMS2 and CFH that determine the risk of AMD may be protective for cCSC.

Diagnosis

Diagnosis of CSC usually begins with a standard examination of the retina, which shows central shallow serous retinal detachment; this is confirmed by optical coherence tomography (OCT), fluorescein, and/or indocyanine green (ICG) angiography, and optical coherence tomography angiography (OCTA). The visual acuity of the affected eye is usually slightly or moderately reduced due to the decreased focal length caused by the raised retina; this phenomenon makes the eye more hyperopic than before.

The use of an Amsler grid can be helpful to confirm suspected macular edema in less overt cases and may help localize the involved area of the visual field. **(**16,17**)** The morphologic changes that occur in eyes with aCSC are the formation of a limited bubble of central serous retinal detachment (Figure 1), RPE detachment, and RPE abnormalities. **(**18,19**)** The outer retinal layers, which include the photoreceptor layer, intermediate line, and inner segment/outer segment (IS-OS) junction, are well-visualized and preserved; occasionally, thickened and hyperreflective tips of detached photoreceptors may be noted. Less frequent findings include focal protrusions of the RPE layer, focal defects in the RPE at the leaking site, minutes fibrinous exudate in the subretinal space, and subretinal precipitates. **(**16,20,21**)** Lastly, an increased choroidal thickness associated with an increased choroidal vascular component is well detectable with enhanced depth imaging (EDI) OCT, predominantly in aCSC forms. **(**22-25**)** The anatomical resolution of subretinal fluid is concomitant with the normalization of the choroidal thickness. **(**26**)**

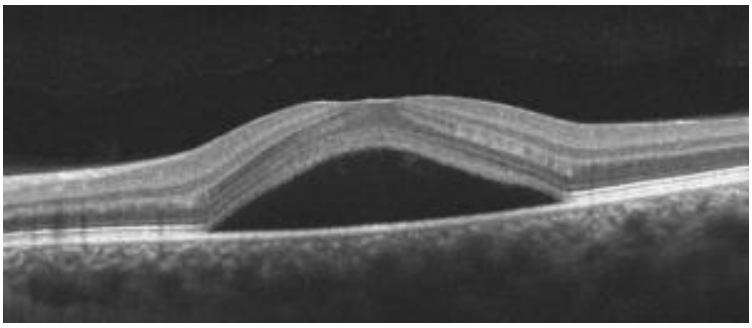

Figure 1

A spectral-domain optical coherence tomography image of an eye affected by acute central serous chorioretinopathy showing a convex-shaped blister of fluid separating the neurosensory retina from the retinal pigment epithelium and choroid. **(**27**)**

The chronic form of CSC exhibits diffuse, rather than focalized, abnormality of the RPE, producing persistent subretinal fluid. The serous detachment in these cases tends to be shallower rather than dome-shaped in comparison with aCSC. Changes in the RPE include low to flat PED, the presence of micro-rips, hypertrophy and atrophy, thickening of the deeper and thinning of the inner choroidal layers, and thinned posterior surfaces of the detached retina with hyperreflective detached photoreceptor tips. In persistent cases, OCT reveals thinning of the outer retinal layers corresponding to the photoreceptor layers, with poor visualization of the IS-OS junction (Figure 2). **(**28**)**

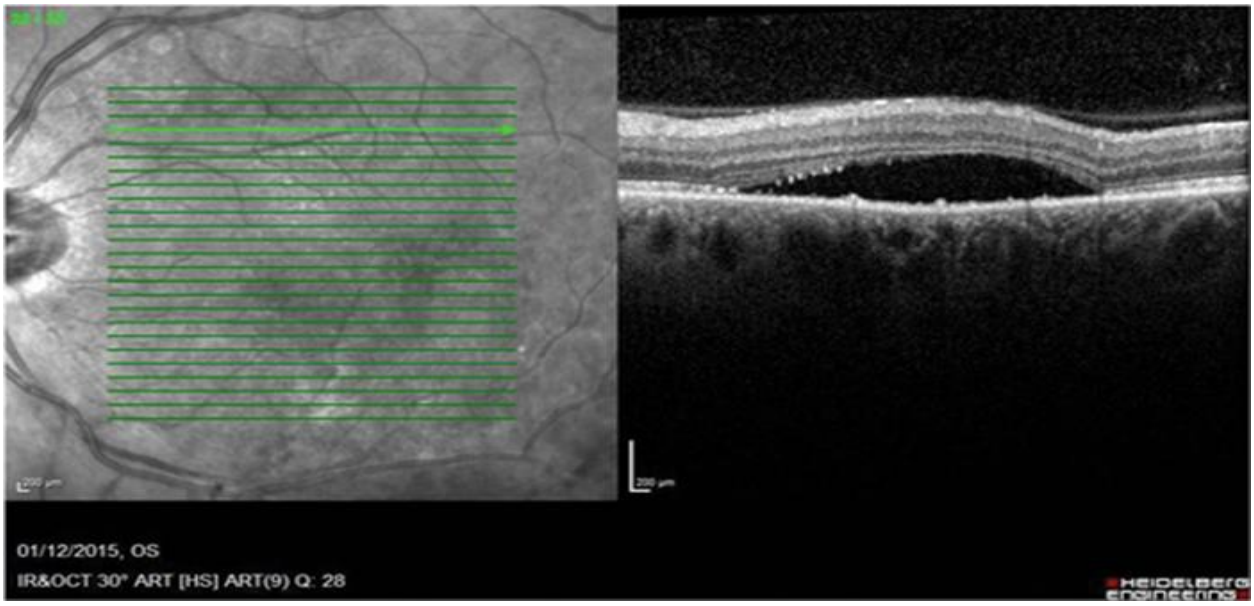

Figure 2

A case of chronic central serous chorioretinopathy (cCSCR)

Fluorescein and ICG angiography allow observation of the fluid leakage from the choroidal vessels, the fluid invasion into the subretinal space, and the choroidal blood vessels. Typically, fluorescein angiography reveals one or more fluorescent “pinpoints” indicating fluid leakage. An expanding point of fluorescein leakage with late pooling into a serous detachment (the classic “smokestack pattern”) is visible in 10–15% of cases (Figure 3). If neuroretinal detachment persists, it tends to move toward the lower part of the macula leading to depigmentation and secondary decompensation of the inferior RPE, resulting in the clinical appearance of gravitational atrophy of the RPE. **(**29**)**

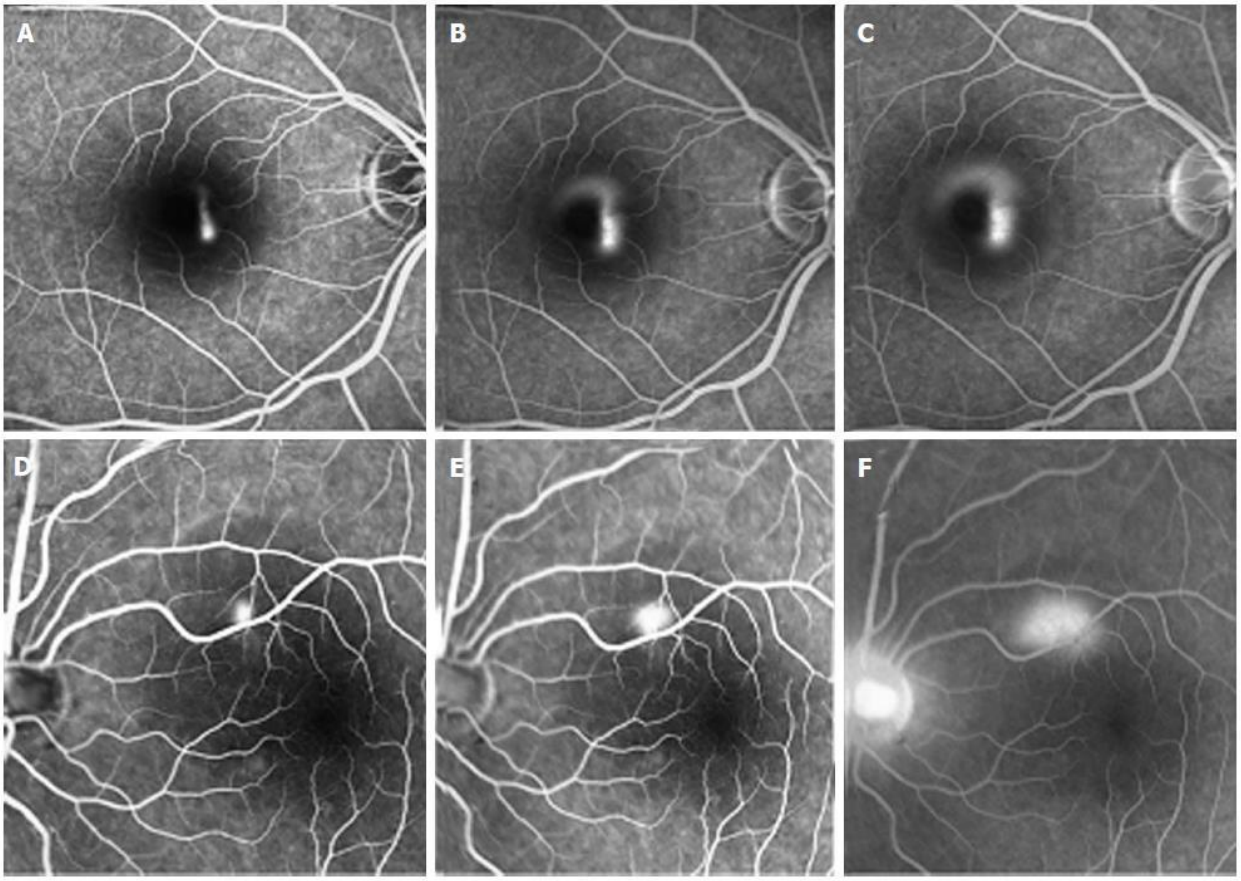

Figure 3

Two different patterns of hyperfluorescent dye leakage on fluorescein angiogram in acute central serous chorioretinopathy; Smokestack pattern of leakage (A, B and C) and inkblot pattern of dye leakage (D, E and F).

Indocyanine green angiography reveals focal delays and hyperpermeability of the choroidal circulation, revealing a delayed initial filling of choriocapillaris arteries in the early phase, and dilation of the

choriocapillaris veins leaking fluid in the subsequent phases. The use of ICG angiography demonstrates that CSC is likely caused by a primary dysfunction of the choriocapillaris; the fluid build-up seems to occur due to small breaks in the RPE, secondary to choriocapillaris disease. **(**30**)**
OCTA reveals areas of focal hypo- and hyper-perfusion in the choriocapillaris. Though, due to the inability to detect plasma flow, OCTA is not suitable to detect leakage points in CSC with confidence. However, OCTA reliably detects choroidal neovascularization (CNV) in CSC even in the absence of exudative activity and may, therefore, represent an important supplement in the diagnosis of CSC. **(**26**)**, **(**31-33**)**

Particularly, OCTA imaging revealed that eyes with CNV complicating CSC exhibited significantly lower choroidal vascular components compared to those with CSC without CNV. **(**34, 35**)**

The prognosis for resolution and visual recovery in patients with aCSC is usually good, thus observation and patient reassurance is considered the best treatment course. Positive converging lenses can be used to improve visual acuity until CSC resolves. Most affected patients recover spontaneously with the improvement of visual acuity, reattachment of the sensory retina, and improvement of the other symptoms within 3–4 months. Conversely, approximately 20–30% of patients will develop one or more recurrences of aCSC, and 5% will develop cCSC. A significant number of these patients develop a limited area of RPE atrophy and depigmentation after the resolution of the affected retinal area.

For patients with CSC, it is important to suspend, or replace with an alternative, any current medications containing steroids, including creams, sprays, and eye drops. In patients treated with corticosteroids, the only suspension of this therapy will be effective in reducing the bullous retinal detachment.

Faster regression of subretinal exudation may be obtained using laser photocoagulation applied to close focal sites of RPE leakage, or by photodynamic therapy (PDT) applied to the areas of choroidal vascular hyperpermeability.

However, a recent meta-analysis concerning the therapeutic interventions for aCSC analyzed 25 randomized clinical trials (RCTs) concluded that it is not completely clear whether a clinically important benefit exists to treating aCSC since it often resolves spontaneously. **(**36**)** Nevertheless, treatment should be considered if resorption does not occur within 3–4 months and in cases of aCSC recurrence in eyes that sustained a permanent visual deficit from a previous episode. Treatment is also suggested in bilateral cases of aCSC, in cases with reduced visual acuity in the fellow eye, and in patients that require

prompt restoration of their vision owing to occupational necessity. The majority of ophthalmologists recommend the treatment of cCSC. **(**37-41**)**

Before the advent of photodynamic therapy, the only treatment option for patients with aCSC was conventional argon laser focal photocoagulation applied to close focal sites of RPE leakage. It consists of light laser treatment that may be applied directly to the point of angiographic leakage if it is located no more than 400 µm from the fovea. Laser treatment consists of a few spots (3–5 impacts) of small diameter (100 µm), low intensity (100–150 mWatt, to achieve a slight whitening of the retina), and short pulse duration (100 mSec). **(**42**)** The laser treatment induces scar tissue formation on the RPE, while coagulating the cluster of diseased RPE cells. It is plausible that the scar restores the RPE barrier to further subretinal fluid accumulation, allowing the pump function of the surrounding healthy epithelium to return the fluid to the choriocapillaris. **(**43**)** Argon laser treatment of the leakage point of the RPE accelerates visual recovery, even though it does not likely improve the final visual outcome significantly. Only selected cases of aCSC may be treated with conventional argon laser therapy; for many cases, the leak is too close to the central macula where photocoagulation would leave a blind spot, or the leakage is too widespread, and its source is difficult to identify. More recently, navigated laser photocoagulation (Navilas® System; GmbH, Teltow, Germany) has improved accuracy and comfort for retinal laser photocoagulation for various retinovascular diseases. **(**44,45**)** In particular, navigated laser photocoagulation, due to its ability of eye-tracking and laser planning on the fluorescein angiography on the same device, can perform precisely targeted treatments thereby reducing iatrogenic retinal damage. **(**46**)**

Photodynamic therapy was introduced as an off-label treatment for both aCSC and cCSC approximately 10 years ago and is applied to the areas of choroidal vascular hyperpermeability. PDT utilizes verteporfin (trade name, Visudyne; Novartis AG, Switzerland), a photosensitive dye that accumulates in abnormal blood vessels. When stimulated by nonthermal red laser light with a wavelength of 689 nm, the presence of oxygen produces many oxygen radicals resulting in local damage to the endothelium and blockage of the abnormal vessels. **(**47.48**)** After the dye infusion, a laser fluence of 50 J/cm2 is directed at the surface of the damaged areas to activate the verteporfin, which triggers a healing mechanism both in the damaged choroidal vessels and RPE. Exploiting the mechanism of causing oxidative damage to the abnormal vessels of the choriocapillaris, PDT induces the absorption of the subretinal fluid and choroidal vascular remodeling with a reduction of choroidal hyperpermeability. **(**49 The efficacy of this treatment, however, is questionable since PDT is suspected of causing choriocapillaris closure and RPE alterations with subsequent damage to the photoreceptors. PDT may also stimulate the upregulation of VEGF and choroidal neovascularization. **(**50, 51**)**

Similarly, subthreshold micropulse laser (SML) therapy is a new treatment that controls the thermal elevation induced by conventional continuous-wave laser photocoagulation. Treatment with an SML reduces the thermal elevation by “chopping” a continuous wave beam into a train of repetitive short pulses, which allows the tissue to cool between pulses, thereby reducing thermal buildup. The rise in temperature in the target tissue remains sub-lethal, but it can create a stress response that induces anti-angiogenic effects. Therapy with an SML consists of using a grid to apply micropulse laser burst to the retinal tissue that causes an approximate 7-°C increase in temperature with each 100-microsecond micropulse. **(**52,53**)** This therapy has been applied to the retina using different lasers with different wavelengths (810, 532, and 577 nm), and it seems that thermal elevation of the retina induces the release of a group of molecules known as heat shock proteins (HSPs) **(**54**)** which are involved in repairing RPE cells and in reducing the inflammatory cascade. **(**55**)** Recently, in comparison to half-dose PDT, the application of 577-nm SML treatment resulted in a slightly greater reduction of the subretinal fluid in patients with chronic CSC. **(**56**)**

Additionally, intravitreal injections of anti-VEGF drugs have been used, off-label, for the treatment of aCSC. This group of drugs effectively reduces choroidal hyperpermeability by blocking vascular leakage. Choroidal hyperpermeability is often associated with increased expression of VEGF, although high VEGF levels are not detected in the aqueous humor of CSC patients. Many reports have demonstrated that therapy with anti-VEGF drugs is effective, with good functional short-term outcomes for treatment of acute and chronic CSC **(**57,58**)** However, during the middle-long term period (six months), low-fluence PDT treatment is more effective than intravitreal anti-VEGF therapy in reducing the subretinal fluid in patients affected by CSC. **(**59**)**

Finally, numerous orally administered drugs have been proposed to treat CSC, including acetazolamide and other diuretics, mineralocorticoid antagonists (spironolactone and eplerenone), 5-alpha reductase inhibitors (finasteride), aspirin, beta-blockers, vitamins, and nonsteroidal anti-inflammatory medications. **(**60**)** All these drugs were found to be most effective in animal and in vitro studies, but none have been shown to have unequivocal benefits in humans.

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