Central Serous Chorioretinopathy

Central serous chorioretinopathy (CSC) is a chorioretinal disease, incompletely understood with systemic associations, a multifactorial aetiology, and a complex pathogenesis.

History

Central serous chorioretinopathy (CSC) was first described by von Graefe in 1866, who named it as ‘relapsing central luetic retinitis’. A variety of names have since been used to describe this idioopathic detachment of the neurosensory retina. It was more than 100 years later that Maumenee, using fluorescein angioscopy, noted that the detachment of the macula resulted from a leak at the level of the retinal pigment epithelium (RPE). Subsequently, Gass provided detailed descriptions of the fluorescein angiographic characteristics of CSC. In 1965 and 1967, the current terms of CSC and idiopathic central serous chorioidopathy (ICSC) were first introduced to describe the same disease.

Although numerous articles and name changes have been published in the ophthalmic literature, the cause, clinical manifestations, natural course, treatment, and the pathogenesis of this condition remains poorly understood, little is known about the long-term natural course, and treatment is based on observational, uncontrolled studies.

Pathogenesis

The pathophysiologic event leading to neurosensory retinal detachment remains unknown, most researchers believe that stasis, ischemia, inflammation, or a combination of the above factors leads to abnormal permeability of the inner choriocapillaries and eventual elevation of RPE and serous retinal detachment. Yet the presence of these pathologic mechanisms in the choroid still cannot replicate the complete constellation of findings in this disorder. In the acute form of the disease, many believe that there is a disruption in the continuity of the detached RPE, leading to focal leakage beneath an overlying neurosensory retinal detachment, the signature of the disorder. This form of mechanical alteration in the integrity of the RPE, referred to as a “blow-out” or “micro rip,” alters its normally impermeable state, leading to serous detachment of the retina. In this sense, the retina seems to be affected only secondarily; whereas the inner choroidal changes represent the primary abnormality of the disorder, leading to the current designation of the disease as central serous chorioretinopathy (CSC). The primary exudative disturbance in the inner choroid, resulting in a macular detachment, is thought to be nonvasogenic, that is, not associated with proliferation of choroidal vessels. The initial avascular nature of CSC distinguishes it from other forms of macular detachment associated with neovascularization of the choroid and eventual disciform scarring.

Corticosteroids, either endogenous or exogenous, have been implicated in this disorder. Jampol et al stated that corticosteroids might sensitize the choroidal blood vessels or RPE to the effects of endogenous catecholamines. They also linked the rapid onset of the non-genomic effects of corticosteroids to the occurrence of serous retinal detachments after the use of high-dose systemic corticosteroids. Carvalho-Recchia et al published the first report of a consecutive series of patients with acute CSC studied prospectively for an association with corticosteroids. They found a statistically significant difference in corticosteroid exposure between study patients and controls. In addition, CSC has been described in patients with endogenously high levels of corticosteroids (Cushing’s syndrome, pregnancy, and stress) as well as in patients with hypercortisolism due to the treatment of ocular (optic neuritis, ischaemic optic neuropathy, solar retinopathy, scleritis, anterior uveitis, and choroiditis) or systemic diseases. Bouza et al suggested a category of systemic diseases that have been associated with CSC only in cases where glucocorticoids were used (such as asthma, allergic rhinitis, sinusitis, myasthenia, back pain). They postulated that glucocorticoid intake in these cases was more important for the development of CSC than the underlying disease itself. Many components of the hypothalamus–pituitary–adrenal axis and the autonomic (sympathetic) nervous system have been implicated in the pathogenesis of CSC.

The other distinguishing characteristic feature noted clinically is the serous pigment epithelial detachment, a clinical manifestation in the fundus that is limited to very few disorders, such as neovascular age-related macular degeneration, polypoidal choroidal vasculopathy and rarely; inflammatory and infiltrative choroidal disorders. More recently, the use of three-dimensional optical coherence tomography (Fourier/spectral domain OCT) has helped investigators to study morphological alterations of the RPE both in symptomatic and asymptomatic eyes of the CSC patients. Not surprisingly, RPE irregularities, at the site of leakage, were noted in symptomatic eyes.

Yoshioka et al observed that intravenous epinephrine produced experimental CSC. They also suggested that...
the serous detachment of the neurosensory retina in CSC was biochemically mediated via stimulation of adrenergic receptors; which resulted in choriocapillary hyperpermeability and degeneration of the RPE cells above the damaged endothelial cells.[17]

The first systematic investigation of the relationship between a type A behaviour pattern (quickness to anger, competitiveness, and need to be in control) and macular disease was conducted by Yannuzzi.[2] This was the first cross-sectional study that employed strict clinical definitions and matched controls to assess CSC patients to classify them as a type A behaviour pattern. The latter was statistically more frequent in CSC patients than in both the control groups used in this study.

Evidence of familial clustering of CSC has been proposed by Weenink et al.[25] They reported 27 patients with characteristic, mostly bilateral, fundus lesions of chronic CSC. Out of 80 investigated relatives, 35 (44%) had fundus lesions: 22 had chronic CSC in one eye, 20 of them had chronic CSC or RPE atrophy in the fellow eye; 13 relatives had RPE atrophy in one or both eyes.

**Pathogenesis Of Visual Loss**

Foveal attenuation, cystoid macular degeneration, secondary choroidal neovascular degeneration, and damage of the foveal photoreceptor layer causes visual loss in CSC.[26,27] Cystoid macular degeneration is generally known as chronic macular oedema, was defined by lida et al.[26] as cystoid spaces without intraretinal fluorescein leakage in the fovea. Posterior cystoid retinal degeneration, generally known as RPE atrophy or decompensation or depigmentation, is defined as cystoid retinal degeneration located in the posterior pole.[28]

One intriguing feature of CSC is the ability of photoreceptors to continue to function above a serous retinal detachment. This is in contrast to the profound visual loss associated with rhegmatogenous retinal detachment.

**Natural history of the disease**

The natural course of acute CSC is believed to be very good with primary cases resolving spontaneously in 3 to 4 months. [7,8] Visual acuity usually recovers well in untreated eyes affected with CSC.[29] However, quality of vision may be affected.30 Patients with resolved CSC may complain of metamorphopsia, decrease in brightness, and alteration in colour vision in the affected eye for several months. Wong et al[31] concluded that ophthalmologists used to ‘trivialize the situation as patients sometimes suffer the consequences following presumed resolution of the disease’. They also found a strong correlation, although statistically insignificant, of visual acuity and contrast sensitivity in both normal and ICSC-affected eyes in their long-term follow-up of resolved ICSC. Koskela et al [32] found a statistically significant correlation between visual acuity and contrast sensitivity after resolution of ICSC. Therefore, clinicians need to be aware that patients may still be visually symptomatic despite visual acuity returning after an episode of ICSC. Yet, a small percentage of cases are known to be associated with recurrent or persistent detachments. In such eyes, the disorder is referred to as chronic CSC, which is arbitrarily defined as detachments lasting 6 months or longer.[33]

**Management Of CSC**

**Investigations**

A good medical history which include history of duration of onset, use of steroids in any form, or systemic diseases which can cause increased catecholamine levels in the circulation and Type A behaviour pattern etc should be elicited.

Base line investigations such as best corrected visual acuity, colour vision, amslers grid charting etc should be performed. Today, current multimode imaging technology is helpful in the evaluation of a patient with CSC.

Fundus fluorescein angiography can demonstrate unifocal or multifocal areas of smoke stack, ink blot or diffuse pattern leaks. Subtle Retinal pigment epithelial detachments may become obvious and retinal pigment anomalies, which may be far more than clinically detected; can be demonstrated with this investigation. This also helps physician to locate the area of leak for treatment.

The use of indocyanine green angiography (ICGA) has revealed staining of the inner choroidal vessels in the mid stages of the study, as islands of indocyanine green (ICG) hyperfluorescence from the posterior pole even to the peripheral fundus.[41] ICGA findings during the middle phase about 10 minutes after the ICG injection were classified as intense or intermediate hyperfluorescence or as having no hyperfluorescence by sawa et al[43] in chronic csc patients. Indocyanine green angiogram helps in locating the area of choroidal hyperpermeability which is the primary pathology, and helps in accurate localization for treatment. Studies have shown that areas of choroidal hyperpermeability may be seen in asymptomatic eyes of patients with CSC and may not correspond to the area of leak on FA and may be further away from it.

OCT is traditionally used to quantify the amount and extent of the subretinal fluid, demonstrate thickening of the neural retina, RPE detachment, subretinal fibrin and is commonly used for monitoring during the follow-up and also for diagnosing the changes in the neurosensory retina that can cause permanent impairment in vision in such eyes. Recently, 3D high-speed OCT has shown to facilitate the understanding of pathophysiologic changes in CSCR. High-resolution optical coherence tomography detects shallow
elevations of the retina, and not surprisingly, a thickening of the choroid.[42] Studies have demonstrated micro rips in RPE; thus throwing light to pathogenic mechanisms. Gupta et al.[14] studied three-dimensional single-layer RPE scans and found that the majority of asymptomatic eyes of CSC patients also showed an uneven RPE surface. This finding was not present in control eyes of healthy volunteers. The authors postulated that accumulation of sub-RPE fluid along with RPE dysfunction, which results in the formation of RPE bumps, visible on spectral-domain OCT, may represent a preclinical or subclinical stage of the disease. Previous studies showed that mERG changes and choroidal permeability changes are present in both affected and fellow eyes of CSC patients.[15,16]

Fundus auto florescence abnormalities in CSC show multiple distinct patterns and seem to provide functional information. Yutaka et al.[44] in their study of 475 eyes with CSC revealed that confluent hypoautofluorescence of the macula, granular hypoautofluorescence of the macula, and increasing age all were independent predictors of decreased visual acuity.

Types of CSC and treatment criteria

It may be important to distinguish CSC into acute and chronic disease even though literature does not give clear cut definitions; as this may correlate with long term prognosis, to decide on the time of initiation of treatment or to wait and watch.

Acute form of the disease is usually self limiting over time with minimal residual changes on imaging. Spade et al.[34] defined chronic CSC as meaning a serous macular elevation, visible biomicroscopically or detected by OCT, that is associated with RPE atrophic areas and subtle leaks or ill-defined staining by Fundus fluorescene angiogram (Fig 1).

The major difference between the two entities as suggested by Pollock et al.[35] where chronic disease is associated with wide spread RPE disturbance without overt detachment in most cases. Chronic detachments and geographic zones of atrophy, produced by antecedent exudative detachments, including those gravitating into the inferior fundus forming RPE tracks (Fig 2), and the acute pigment epithelial leak at the edge of a pigment epithelial detachment, have been noted. In acute cases one may see focal RPE disturbances with marked detachment. Diffuse RPE or sick RPE syndrome is a term that has been defined in literature as chronic CSC by some investigators[35] or as a form of chronic CSC by others. It has been reported as an idiopathic condition or as a complication of systemic corticosteroid treatment.[35] Its natural course is favourable despite the remaining problems in colour vision and some degree of metamorphopsia.

Bullous serofibrinous exudative retinal detachment occurs in some patients with CSC which may pose diagnostic dilemma. Corticosteroid therapy, organ transplantation, haemodialysis, and pregnancy have been reported to be associated with this form of CSC. It has been described however as an idiopathic CSC form as well.[37,38,39] In the largest case series of ICSC with spontaneous bullous exudative RD, visual prognosis was good without any treatment.[40]

Photoreceptor atrophy at the fovea, despite successful reattachment, occurs after duration of symptoms of approximately 4 months.[45] Thus treatment should be considered in recurrent chronic CSC or a single CSC episode, of greater than 3 months duration, with some signs of chronic CSC.

Previous permanent visual loss in the fellow eye caused by a similar procedure would also indicate that treatment should be instituted even in the absence of chronic CSC signs or even if foveal photoreceptors were not immediately threatened.
tubercular drugs, insulin-free pancreatic extract, and thyroid extract have all also been suggested in the past. The role of stimulation of adrenergic receptors in the pathogenesis of CSC led some investigators to suggest that b- or a-adrenergic blockade could be utilised in the treatment of CSC. Acetazolamide has also been tried as a means of treatment of the chronic macular oedema caused by CSC or other chorioretinal diseases with short-term encouraging results but no evidence of long-term benefit. However, there is no significant proof to support such therapeutic approaches.

**Current and future treatment options for CSC**

**Laser photoocoagulation**

Robertson and Ilstrup46 suggested a reduction in CSC recurrences and shortening of the duration of detachment with direct laser photoocoagulation compared with sham or indirect (away from the site of leakage) photoocoagulation within a follow-up period of 18 months. Dellaporta[47] concluded that untreated eyes were 3.3 times more likely to develop recurrence than treated eyes. Gilbert et al[48] found no difference either in final visual acuity or in recurrence rate between eyes treated with argon laser photoocoagulation and untreated eyes in their retrospective long-term follow-up study of CSC patients. They also explained discrepancies in recurrence rates in various studies by the different follow-up durations and different treatment techniques (laser spot size).

In the study, with the longest follow-up (6–12 years), argon laser photoocoagulation treatment was not shown to reduce the incidence of recurrent disease or of chronic CSC. This study also showed that the role of argon laser photoocoagulation in CSC with good visual acuity is limited to hastening relief of symptoms by achieving speedier resolution of serous detachment.[49]

Thus with the current level of evidence one may conclude that treatment is mainly effective in acute csc with focal leaks seen on FFA; in faster resolution of subretinal fluid and symptoms when compared to the natural history of the disease. However, if the area of leakage is subfoveal or juxtafoveal, photoocoagulation may induce secondary choroidal neovascularisation (CNV) and/or of damage foveal photoreceptors.[50] Therefore other treatment options appear safer.

**Transpupillary thermotherapy**

Shukla et al [51] performed TTT in long-standing CSC, which resulted in the resolution of CSC with subfoveal angiographic leaks and significant improvement in visual outcome, in comparison with the natural history of persistent CSC. Long-term results are unknown.

**Discontinuation of corticosteroids**

Sharma et al[52] reported an observational case series of atypical severe CSC treated with corticosteroids for their ocular condition. Discontinuation of corticosteroids resulted in reattachment of the retina in 88% of affected eyes. They concluded that discontinuation of corticosteroids in atypical CSC could lead to obliteration of RPE leaks and retinal reattachment without laser treatment.

**Photodynamic Therapy**

Chan et al[53] postulated that PDT could be beneficial for the treatment of CSC by its effect on the structure of choroidal vasculature, causing alterations in choroidal permeability. Both Fluorescein and ICG-A-guided PDT have been recommended for treatment of CSC. Choroidal hypoperfusion, which is the main mechanism of action of PDT in CSC, can also lead to complications, especially if conventional PDT is performed. This led investigators to reconsider PDT parameters for the treatment of CSC. Lai et al54 reduced the dosage of verteporfin and shortened the interval between infusion and laser application to induce choroidal vascular remodelling and they also found that it is safe and effective in acute and chronic cases.

Reibaldi et al[55] described two cases of long-standing CSC treated with ICG-A-guided low-fluence PDT with good anatomical and functional results. The anatomic and functional outcomes were encouraging. They also studied the efficacy of ICG-guided low-fluence PDT compared with standard PDT in a prospective non-randomised clinical trial which showed equal efficacy. They postulated that choroidal hypoperfusion related to PDT could be reduced by low-fluence PDT.[56] Recently, Inoue et al[57] shortened the irradiation time and reduced the total energy using the same light intensity and the same verteporfin dosage as the standard protocol.

Maruko et al,[58] showed that the choroidal thickness and hyperpermeability seen during ICG-A was reduced after PDT. They suggested that PDT reduces the choroidal vascular hyperpermeability seen in CSC and it may act by a different mechanism than laser photoocoagulation. Most published studies suggest PDT with verteporfin is a safe and efficacious treatment even in chronic CSC and that complications are rare. Unlike argon laser photoocoagulation, it can be performed for subfoveal leakage too. (Figure 3a and b).
Fig 3a. Pre Low fluence Photodynamic therapy Colour fundus and FFA images of a case of chronic CSC with multifocal areas of leaks including subfoveal leaks.

Pre PDT OCT BCVA 4/60 <N 36

Post PDT 7 Days

Post PDT 14 DAYS

Post PDT 30 days BCVA 6/18 N12

Fig 3b. Pre and serial post low fluence PDT Oct images showing complete resolution of sub retinal fluid in 4 weeks
**Micropulse diode laser photoacoagulation**

Sub threshold micropulse diode laser (810 nm) has recently been assessed for the treatment of chronic CSC [59,60]. It scores over conventional laser in having minimal or no collateral damage. It has been used in chronic disease with definite leak or diffuse leak. In the largest series reported; visual gain of 2 to 3 lines were observed in 58 % of the patients. ICG assisted subthreshold micropulse photoacoagulation was assessed by Ricci et al [60] in chronic CSC and they found beneficial effect from this treatment but with incomplete recovery in 1 year. It was found not superior to PDT.

Thus to conclude; subthreshold micropulse laser is found to be safe and effective in chronic CSC and may be considered as an alternative to PDT is cases with well defined or focal areas of leak. They seem to be ineffective in diffuse area of leakage and sick RPE syndrome. Larger, controlled, randomised clinical trials are needed to establish their definitive role.

**VEGF Antagonists**

The hypothesis that VEGF inhibitors can reduce choroidal vascular permeability and ischemia has led some investigators to use intravitreal bevacizumab in acute and chronic CSC [61,62]. However, all of the related reports are small, uncontrolled case series with a short duration of follow-up; larger, controlled trials are still needed to evaluate the efficacy and safety of anti-VEGF agents for this disease.

**Corticosteroid antagonists**

The role of corticosteroid antagonists in treating CSC was first proposed by Jampol etal. [63] This was based on endogenous hypercortisolism in patients with CSC. The potential treatment of CSC episodes using antiglucocorticoid agents includes RU486 (mifepristone) and ketoconazole.

It was first tested as a potential treatment for CSC by Golshahiet al [64] in a prospective, case-controlled study which they did not show any conclusive benefit. Meyerle et al 65 found a delayed therapeutic response at 8 weeks after initiation of treatment with increasing the dose of ketoconazole.

**Asprin**

Diseases associated with CSC, plasminogen activator inhibitor-1 (PAI-1) was increased and that aspirin is effective in lowering PAI-1 levels and platelet aggregation made some physicians to evaluate its role in this disease. Caccavale et al [66] evaluated low-dose acetyl salicylic acid (aspirin) in 107 CSC patients with a mean follow-up time of 20 months. They found a rapid recovery of visual acuity and a reduced number of recurrences in their patients.

**Conclusions**

CSC definitely seems to be a multifactorial disease with systemic association and multiple etiopathogenesis which ultimately lead to bilateral disease. As for today we need large, prospective or even retrospective long term follow-up studies to decide on one or more safe and effective forms of treatment, which will be generally accepted by clinicians. Until then, it seems reasonable to suggest reduced dose/fluence/irradiation time verteporfin PDT in recurrent chronic CSC or in single CSC episodes, not resolving for a period of at least 3 months, accompanied by signs of chronic CSC. In both of which there is active leakage involving the fovea or a juxtafoveal area. The success seen in treating islands of active or intense staining in the inner choroid with ICGA-guided PDT has also led clinicians to treat focal RPE leaks near the fovea with fluorescein guidance. These leaks are known to occur in association with ICG inner choroidal staining and will respond well to PDT without leaving the photoagulative legacy of photoreceptor and RPE degeneration and the accompanying visual scotoma. Caution in treating such leaks near the fovea is appropriate when there is accompanying fibrin visible on clinical examination because of the potential for an exaggerated response. ICGA-guided therapy remains the best approach for clinicians to consider for eyes with chronic CSC, particularly if they demonstrate intense or intermediate ICGA hyperfluorescence patterns in the choroid and persistent or progressive detachment with associated degenerative changes in the RPE and photoreceptors accompanied by vision loss. Micropulse diode laser treatment, applied on well defined leaking sites, can be considered as an alternative. The use of corticosteroid antagonists, possibly after evaluation of patients’ cortisol profile (for example, urine cortisol or tetrahydroaldosterone levels), is an interesting future option that merits further investigation. In addition, counselling about discontinuation of steroid treatment in any form for systemic or ocular conditions and explanation of the relation of the disease to stress is helpful in the management of CSC patients.

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