Management of Chronic Central Serous Chorioretinopathy

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- Research Support: Optos, Notal Vision
- *Off label use of PDT and bevacizumab will be discussed*
ETIOLOGY
There are only two times I feel stress:

Day and Night.
“Type A” Personality

- Exacting
- Demanding
- Impatient
- Competitive
- Conscientious
- Reliable
- High energy
- Obsession with achievement
Stress/Type A

- Effects on hypothalamus-pituitary-adrenal gland axis
- Increased secretion of glucocorticoids
- Manifest in susceptible individuals as CSC
Systemic Causes of CSC

- Bone marrow transplantation
- Solid organ transplantation
- Lupus
- MPGN type II
- H. pylori infection
- Pregnancy
CSC in Women

- 84 eyes in 78 women with CSC
- Mean age: 47 yrs (31-71 yrs)
- 62% achieved complete recovery over a median of 5 months (range: 2 – 108 mos)
- More likely to resolve completely with
  - shorter duration
  - single occurrence
  - subretinal precipitates
  - absence of PED
  - lack of hormone replacement therapy
  - < 50 years of age

Medications Associated with CSC

- Medications with sympathomimetic properties
- A concomitant psychogenic stress and high-dose ingestion of:
  - Pseudoephedrine
  - Oxymetazoline nasal spray
  - 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy)
- Increase in choroidal blood flow induced with sympathomimetics may have a role in the development or exacerbation of CSC
• 27 yo WM c/o visual loss OD beginning 3 days ago
• Began “after hangin’ out with my buddies, drinking and stuff”
• Yes, it has happened before
• VA: 20/25 OD and 20/20 OS
• Patient was advised to stop “partying”
• 6 weeks later:
  ▪ VA: 20/20-1 OD
CSC Associated with Sildenafil (Viagra®)

- NAION
- “blue vision”
- About a dozen cases of sildenafil associated CSC in the literature
Steroid Associated CSC

- Endogenous and exogenous corticosteroids are implicated as a causative factor.
- May sensitize the choroidal blood vessels or RPE to the effects of endogenous catecholamines.
- Corticosteroids are contraindicated in CSC.
- Try to discontinue or reduce the steroid dosage.
DIAGNOSIS
CSC
Fluorescein Angiography
Chronic CSC
Indocyanine Green Angiography

- The disease is at the level of choriocapillaris
- Helpful in distinguishing vascular from avascular PED
- Helpful in distinguishing CSC from other diseases
  - Polypoidal Choroidal Vasculopathy
Auto-fluorescence: Chronic CSC
Retina elevated without cystic edema overlying NSD. Photoreceptor outer segments continue to grow.
CSC: Enhanced Depth OCT

**NORMAL**
Typical ED-OCT
Choroidal thickness
297 μm

**CSC Patient**
Typical ED-OCT
Choroidal thickness
505 μm

Asymptomatic patient without fluid
CSC: Choroidal Thickness

**CSC Pt. #1 with NSD**
ED-OCT
Choroidal thickness
539 μm

**CSC Pt. #2 with NSD**
ED-OCT
Choroidal thickness
609 μm
Central Serous Chorioretinopathy (CSC)

- Some patients can develop chronic neurosensory detachments
- Chronic or recurrent CSC can cause severe, permanent vision loss
Historical Managements

- Psychotherapy
- Corticosteroids
- Adrenocorticotropic hormone
- Anti-inflammatory drugs
- Retrobulbar tolazoline injections
- Subconjunctival injections of milk, albumin and salt solutions
- Anti-syphilitic drugs
- Anti-tubercular drugs,
- Insulin-free pancreatic extract
- Thyroid extract
- $\beta$- or $\alpha$-adrenergic blockade
- Acetazolamide
- Low-dose acetyl salicylic acid (aspirin)
Glucocorticoids – in all forms:

- Oral, intravenous, intramuscular steroids
- Topical steroid cream and shampoos
- Pulmonary steroid inhaler & nasal spray
- Intra-articular steroid injection
- Periocular & intravitreal steroid injection
Chronic CSC Management Options

- Focal leak located well away from the fovea
  - Thermal laser photocoagulation
    - Conventional laser
    - Micropulse laser
To avoid the high peak temperatures necessary with a single continuous wave laser, multiple pulses with subthreshold energies are applied.
- It has been shown that when pulse duration is in the order of microseconds, the retina can be spared from damage.
- In animal models, selective laser treatment of RPE was possible.

Micropulse Subthreshold Laser


Management Options

- Chronic CSC
  - Photodynamic therapy (PDT)
    - Reported use since 2003
PDT for Chronic CSC
PDT for Chronic CSC

1 MONTH LATER

ICG
PDT for CSC

PRE TREATMENT

1 MONTH LATER
Complications of PDT in CSC

- RPE rip
- RPE atrophy
- RPE clumping
- Choroidal ischemia
- Choroidal neovascular membrane
2 weeks after PDT
“Standard” PDT Parameters

- 6 mg/m²
- 600 mW/cm²
- 50 J/cm²
- 83 seconds

In order to avoid PDT-related complications, PDT with half-dose verteporfin or half-fluence energy or half-time for treatment of chronic idiopathic CSC have been reported.
Photodynamic Therapy for Chronic or Recurrent Steroid Associated Central Serous Chorioretinopathy

Tae-Gon Lee, MD and Judy E. Kim, MD
Br J Ophthalmol. 2010

- Evaluated the short term efficacy of PDT for steroid associated chronic or recurrent CSC
- Retrospective review of 9 consecutive cases of steroid associated CSC treated with PDT using
  - Full-fluence for *extrafoveal* treatments (n=5)
  - Half-fluence for *fovea involving* treatments (n=4)
  - Treatment based on leakage seen on FA
- Serous retinal detachment disappeared in all cases following PDT without any complications with a mean follow up of 8 months.
- One patient who was treated with reduced fluence PDT had a recurrence at 6 months and was retreated.
- Mean BCVA at baseline = $20/83$ (LogMAR 0.62).
- Mean BCVA at last follow-up = $20/47$ (LogMAR 0.37) ($p=0.05$).
- Visual acuity improved by $\geq 2$ lines in 3 (33%) eyes.

Chronic CSC Management Options

- Photodynamic therapy (PDT)
- Micropulse laser
- Intravitreal bevacizumab (Avastin)
Bevacizumab for CSC

Bevacizumab for CSC

- VEGF and IL-8 were **not increased** in the aqueous humor and plasma of 12 patients with CSC when compared with control group.
- The effect of intravitreal bevacizumab injection as a treatment for CSC must be fully understood.
- “The true effect of anti-VEGF treatment in patients with CSC remains to be elucidated.”

Lim JW, et al. Aqueous humor and plasma levels of vascular endothelial growth factor and interleukin-8 in patients with central serous chorioretinopathy. Retina 2010:30;1465-71
Other Experimental Options: Glucocorticoid Antagonists

- **Ketoconazole**: an oral antifungal drug that has been shown to be a potent dose-dependent inhibitor of gonadal and adrenal steroid synthesis; treatment of Cushing’s syndrome, prostate cancer
Mifepristone (RU-486)

- Potent glucocorticoid receptor antagonist
- FDA approved as an abortifacient
- Orally bioavailable
- Minimal side effects
  - skin rash
  - reversible liver enzyme elevation
- Investigated for:
  - Cushing’s disease
  - meningioma
  - uterine leiomyomata
  - Depression
Other Experimental Options

- **Rifampin**: an antituberculosis medication; has the ability to decrease endogenous steroid production
Other Experimental Options

- **Methotrexate:**
  - Weekly, low dose, oral methotrexate in 9 patients with chronic CSC with a mean duration of 28 months
  - 5-10 mg/week
  - Mean duration of treatment: 89 days
  - Mean VA improved from 20/67 to 20/35 at 8 weeks
  - 83% had resolution of SRF

Oliver AL, et al. Low dose oral methotrexate for the treatment of chronic CSR. ASRS 2011
Antimineralocorticoid Agents

- Spironolactone (Aldactone)
- Eplerenone (Inspra)
  - Potassium sparing diuretics
  - Treatment of heart failure
Summary: Management of Chronic CSC

- For chronic or recurrent CSC, various treatment options can be considered.
- Reduced fluence PDT may be preferred in fovea involving cases.
- Further studies on best treatment parameters with PDT, micropulse laser, and glucocorticoid antagonists for CSC are being performed.
- Other treatment modalities are being investigated.
Question patients about medications
  - Steroids: all routes of drug delivery
  - Sympathomimetics: over the counter, recreational

Advise patients with CSC to discontinue or lower the dosage of these medications

Identify potential systemic risk factors for CSC
  - Cushing’s syndrome
  - Organ transplantation
  - Stress
RELAX
because sometimes a galactic war has to take a break.

Tranquility Sounds

STOP STRESS
Stress Reduction Kit

1. Place kit on FIRM surface.
2. Follow directions in circle of kit.
3. Repeat step 2 as necessary, or until unconscious.
4. If unconscious, cease stress reduction activity.
THANK YOU!
CSC Associated with Sildenafil (Viagra®)

- NAION
- “blue vision”
- 11 cases of sildenafil associated CSC
• 35 year old money market manager
• CC: blurred vision, image size difference, headache and eye strain for 1 month
• No medical problems
• No medications
• VA: 20/15, 20/25
• Under stress? Yes
• Type A personality? Yes
First described by von Graefe in 1866: ‘relapsing central luetic retinitis’

In 1927, psychogenic-related hypothesis proposed by Horniker

Infections, toxins, an immunological reaction, neuronal, circulatory, and hormonal regulatory factors have all been implicated in the initiation of the damaging process that leads to CSC
CSC has been described in patients with endogenously high levels of corticosteroids (Cushing's syndrome, pregnancy, and stress)\cite{39} as well as in patients with hypercortisolism due to the treatment of ocular (optic neuritis, ischaemic optic neuropathy, solar retinopathy, scleritis, anterior uveitis, and chorioretinitis)\cite{83-88} or systemic diseases.\cite{89,90}

Jampol et al.\cite{81} stated that corticosteroids might sensitise the choroidal blood vessels or RPE to the effects of endogenous catecholamines.
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.\cite{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.
As a result of the multiple theories and despite CSC having a favourable natural course, various treatments have been proposed. Psychotherapy was suggested in 1948, [40] followed by drug therapies such as α-adrenergic blockade, [41] β-adrenergic inhibitors, [42] and acetazolamide. [43] Laser treatments have included retinal photocoagulation, [44-47] transpupillary thermotherapy (TTT), [48] and currently photodynamic therapy (PDT). [49-53] More recently, anti-VEGF agents [54-57] and corticosteroid antagonists [58,59] have also been investigated.
Photoreceptor atrophy in the fovea, despite successful reattachment, occurs after duration of symptoms of approximately 4 months.
The term acute CSC usually refers to the self-limiting CSC that resolves spontaneously over a few months without any treatment and minimal residual changes on imaging.
chronic CSC, 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 FA. Polak et al [36] noted that the major distinction between chronic and acute disease is the fact that chronic disease has widespread pigment epithelial changes without overt detachment in most cases, whereas in acute disease there is focal pigment epithelial abnormality and marked detachment.
, 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
• Psychotherapy
• Corticosteroids
• Adrenocorticotropic hormone
• Anti-inflammatory drugs
• Retrobulbar tolazoline injections
• Subconjunctival injections of milk, albumin and salt solutions

• Anti-syphilitic drugs
• Anti-tubercular drugs,
• Insulin-free pancreatic extract
• Thyroid extract
• $\beta$- or $\alpha$-adrenergic blockade
• Acetazolamide
• Low-dose acetyl salicylic acid (aspirin)
The multifactorial aetiology and complex pathophysiology of the disease and its generally favourable natural history provide no clear proof of the necessity and long-term efficacy of any of the treatment choices that have been reviewed in this article.
After reviewing the voluminous literature on the aetiology and pathogenesis of CSC it certainly seems that CSC is a multifactorial disease. It appears to result from a complex interaction of known and unknown environmental and genetic factors. This ultimately leads to a bilateral disease with systemic associations.

In 1986, Yannuzzi\textsuperscript{[2]} stated there was a lack of a definitive, universally accepted treatment for CSC. This could also be stated today. The multifactorial aetiology and complex pathophysiology of the disease and its generally favourable natural history provide no clear proof of the necessity and long-term efficacy of any of the treatment choices that have been reviewed in this article. Further large, prospective or even retrospective long-term follow-up studies are required 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. 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 for systemic or ocular conditions and explanation of the relation of the disease to stress is helpful in the management of CSC patients.
Central Serous Chorioretinopathy (CSC)

- Characterized by development of serous neurosensory retinal detachment at the posterior pole
- Usually resolves spontaneously within 3 to 4 months
- Majority of patients recover baseline visual acuity
Central Serous Chorioretinopathy (CSC)

- Some patients can develop chronic neurosensory detachments
- Chronic or recurrent CSC can cause severe, permanent vision loss
CSC
Fluorescein Angiography
Indocyanine Green Angiography

- The disease is at the level of choriocapillaris
- Helpful in distinguishing vascular from avascular PED
- Helpful in distinguishing CSC from other diseases
Autofluorescence: Acute CSC
Auto fluorescence: Acute CSC

FA

AF
Autofluorescence: Chronic CSC
Optical Coherence Tomography
Choroidal Thickness

- Enhanced depth imaging spectral-domain OCT demonstrated a very thick choroid in patients with CSC
- The choroidal thickness measured in 28 eligible eyes of the 19 patients was 505 um, which was significantly greater than the choroidal thickness in normal eyes
- This finding provides additional evidence that CSC may be caused by increased hydrostatic pressure in the choroid

Management Options

• Acute
  • Observation

• Focal leak located well away from the fovea
  • Laser photocoagulation
    • Conventional laser
    • Micropulse laser
Micropulse Laser

Continuous Wave Laser

Micropulse Laser

To avoid the high peak temperatures necessary with a single continuous wave laser, multiple pulses with subthreshold energies are applied.
• It has been shown that when pulse duration is in the order of microseconds, we can spare the retina from damage
• In animal models, selective laser treatment of RPE was possible

Micropulse Subthreshold Laser

Management Options

- Chronic CSC
  - Photodynamic therapy (PDT)
    - Reported use since 2003
PDT for Chronic CSC

- 82 eyes of 72 patients with chronic CSC treated by conventional PDT
- Mean follow-up of 12 months
- Mean logMAR BCVA changed from 0.53 before PDT to 0.48 at 6 months (p = 0.007) and 0.37 at the end of follow-up (p < 0.0001)
- Macular detachment was resolved and subretinal fluid disappeared in all cases
- No cases developed severe vision loss
- Reactive RPE hypertrophy appeared in 9 cases after PDT

Complications of PDT

- RPE rip
- RPE atrophy
- RPE clumping
- Choroidal ischemia
- Choroidal neovascular membrane
“Standard” PDT Parameters

- 6 mg/m²
- 600 mW/cm²
- 50 J/cm²
- 83 seconds
Chronic CSC: Photodynamic Therapy

• In order to avoid the PDT-related complication, PDT with half-dose verteporfin or half-fluence energy for treatment of chronic idiopathic CSC has been reported.

• Among 48 eyes in the study with a mean follow up of 12 months, Chan and colleagues found complete resolution of serous retinal detachment in 90% of eyes and stable or improved vision in 96% of eyes following PDT using half-dose verteporfin for chronic idiopathic CSC.

Full-fluence vs. Low-fluence PDT

- 42 cases in a prospective, multicentre clinical trial with 12 months follow-up
- Both standard-fluence (n=19) and low-fluence PDT (n=23) resulted in complete SRF reabsorption with visual acuity improvement in most of the eyes
- However, choroidal hypoperfusion related to PDT was more likely with standard-fluence and could be reduced by low-fluence PDT

Full-fluence vs. Reduced-fluence PDT

What if …

- Treat with full-fluence when laser spot to treat the leakage does not include the fovea
- Treat with reduced-fluence when laser spot to treat the leakage includes the fovea
Photodynamic Therapy for Steroid Associated Central Serous Chorioretinopathy

Tae-Gon Lee, MD and Judy E. Kim, MD
Steroid Associated CSC

- Endogenous and exogenous corticosteroids are implicated as a causative factor.
- Corticosteroids are contraindicated in CSC.
- CSC may not resolve despite discontinuing steroids or continued use of corticosteroids may still be necessary.
- Recurrent or chronic CSC can be difficult to manage and possibly result in irreversible vision loss.
• Evaluated the short term efficacy of PDT for steroid associated chronic or recurrent CSC
• Retrospective review of 9 consecutive cases of steroid associated CSC treated with PDT using
  • Full-fluence for extrafoveal treatments \( (n=5) \)
  • Half-fluence for fovea involving treatments \( (n=4) \)
  • Treatment based on leakage seen on FA
• All had documented history of CSC greater than 1 year
• The mean duration of the current episode of CSC prior to PDT were 45 months (range: 3-131 months)
• 6 (67%) had history of 3 or more recurrences of CSC
• 3 (33%) patients had active bilateral CSC, while 4 (44%) patients had macular pigmentary abnormalities in the fellow eye
• Only 1 eye was treated with PDT in each case
• Serous retinal detachment disappeared in all cases following PDT without any complications
• One patient had a recurrence at 6 months and was retreated
• Mean BCVA at baseline = 20/83 (LogMAR 0.62)
• Mean BCVA at last follow-up = 20/47 (LogMAR 0.37) (p=0.05)
• Visual acuity improved by ≥ 2 lines in 3 (33%) eyes
- Yannuzzi and colleagues addressed the importance of ICG angiography and ICG-guided PDT for the treatment of chronic CSC
- Taban et al. and Ruiz-Moreno et al. reported good results with PDT based on FA findings only for the treatment of chronic CSC
- We also performed PDT based on FA findings and achieved favorable results
- Although ICG-guided PDT is a rational approach, PDT based on FA findings also seems to be effective
PDT Treatment Variables

- Full vs. half fluence (50 J/cm² vs. 25 J/cm²)
- Standard vs. half time (83 seconds vs. less)
- Full vs. half dose of verteporfin
- Treat based on ICG vs. FA
- Treat entire area of neurosensory detachment vs. area of leakage only
ICG for Prognosis

- Investigated which patients with CSC respond best to PDT based on ICG characteristics
- Success rate appeared to depend on the degree of vessel hyperpermeability seen on ICG
- PDT not effective or recurrence rate was high in eyes without intense hyperfluorescence on ICG
- PDT most effective in eyes with significant leakage seen in the late frames of ICG

Management Options

- Chronic CSC
  - Photodynamic therapy (PDT)
  - Intravitreal bevacizumab (Avastin)
Intravitreal Bevacizumab

Intravitreal Bevacizumab

- 30 patients with CSC of at least 3 months' duration
  - **Treatment Group**: 15 patients treated with 2.5 mg/0.1 ml bevacizumab
  - **Control Group**: 15 patients observed

- At 6 months, resolution of neurosensory retinal detachment in 12 (80%) eyes in the treatment group and 8 (53%) eyes in the control group (P < 0.01)

- All 15 (100%) treated eyes had stable or improved vision, compared with 10 (67%) eyes in the control group (P < 0.01)

Management Options

• Acute
  • Observation

• Focal leak located well away from the fovea
  • Thermal laser photocoagulation
    • Conventional laser
    • Micropulse laser
• **Corticosteroid Antagonists** Jampol *et al*[^81] first suggested that glucocorticosteroid antagonist activity may be of value in preventing or treating episodes of CSC. This was based on the association of endogenous hypercortisolism with the development of CSC.[^39] The potential treatment of CSC episodes using antiglucocorticoid agents includes RU486 (mifepristone) and ketoconazole.

• RU486 is an active anti-glucocorticosteroid and anti-progesterone agent. This dual action results from similarities between receptors involved.[^153] Its use in voluntary early pregnancy termination has delayed the initiation of ophthalmic clinical trials in the United States.
Ketoconazole is also an adrenocorticoid agent. It was first tested as a potential treatment for CSC by Golshahi et al,\textsuperscript{[58]} in a prospective, case-controlled study. Patients received 200 mg of the drug per day for 4 weeks. The clinical benefit of this trial was not statistically significant. After 3 years, an increase in dosage of ketoconazole to 600 mg daily for 4 weeks was tried by Meyerle et al \textsuperscript{[59]} who found a delayed therapeutic response at 8 weeks after initiation of treatment. They postulated that their inconclusive results were because of short duration of treatment or/and normal baseline cortisol levels of the patients involved and they suggested larger, controlled trials to test the efficiency of ketoconazole in CSC patients.
Summary

- For chronic or recurrent CSC, PDT is a treatment option
- PDT can effectively treat steroid associated CSC at least for short-term
- Best treatment parameter for PDT is still being studied
- Other treatment options include intravitreal bevacizumab
• 27 yo WM c/o visual loss OS beginning 3 days ago
• Began “after hangin’ out with my buddies, drinking and stuff”
• Yes, it has happened before
• Va 20/25 OD and 20/20 OS
• Patient was advised to stop partying
• 6 weeks later:
  • Va 20/20-1 OD
A simple case of CSC?

- “type A personality”
- steroids
- MGPN II glomerulonephritis
- H. Pylori infection
- anything else???
CSC Associated with Sildenafil (Viagra®)

- NAION
- “blue vision”
- 11 cases of sildenafil associated CSC
Other Uses of Sildenafil (Viagra®)

- Pulmonary hypertension (Revatio)
- Altitude sickness
- ? Enhance sports performance
- Recreational use: “sextacy” mixed with ecstacy, “rockin’ and rollin’” and “trail mix”
- Prevent flowers from wilting (up to 2 weeks)
- 2007 Nobel Prize in Aviation: aids jet lag in hamsters
CSC Associated with Sildenafil (Viagra®)

- Originally developed to treat angina and hypertension
- Increases the release of nitric oxide
- Effect on choroidal vasculature?
  - McCulley: increase in choroidal thickness (mean 33%, median 9%)
  - Quiram: engorgement of the choroidal vasculature
  - Metelitsina: no change in foveal circulation in eyes with AMD
- Consider sildenafil in (refractory) cases of CSC
• Yannuzzi LA. Type A behavior and central serous chorioretinopathy. Retina 1987;7:111-131.
Although the precise pathophysiologic events leading to macular detachment are still poorly understood, the clinical manifestations begin with a disturbance in the retinal pigment epithelium which alters its normally impermeable state so that fluid leakage occurs, producing detachment of the retina itself. In this regard, the retina appears to be affected only secondarily. It is currently believed, according to research by our group, that the choroidal circulation develops a pool of extracellular fluid or edema. This intrachoroidal edema or leakage exerts pressure on the pigment epithelium, causing it to blister–up into focal or multifocal elevations known as serous detachments of the pigment epithelium. The blister disrupts or develops a mechanical opening, usually at the junction between its elevated and attached areas, permitting fluid to leak through the pigment epithelium beneath the neurosensory retina. This leakage is called “avascular” since it is not associated with the proliferation of an abnormal blood vessels (neovascularization) as is typical in the wet form of age–related macular degeneration. It is important to keep in mind that neovascularization may occur even in a patient with central serous chorioretinopathy as a secondary complication. So, while central serous chorioretinopathy is associated typically with non–vascular leakage, vascular leakage may evolve. One of the challenges in diagnosing central serous is distinguishing between these two types of leakage, especially in middle–age and older–age patients who are at risk for both central serous and age–related macular degeneration.
CSC in Women

- 84 eyes in 78 women with CSC
- 62% achieved complete recovery over a median of 5 months (range: 2 – 108)
- 88% had a final vision of 20/40 or better. Episodes associated with subretinal precipitates ($P = 0.001$), single occurrence ($P = 0.002$), absence of hormone replacement therapy (HRT) ($P = 0.01$), duration less than 5 months ($P = 0.02$), or absence of a pigment epithelial detachment (PED) ($P = 0.05$) were more likely to completely recover. Recurrence ($P = 0.03$) and lack of subretinal precipitates ($P = 0.03$) were associated with a final vision less than 20/40. Age over 50 ($P = 0.004$) and the presence of a PED ($P = 0.02$) were associated with duration longer than 5 months. **Conclusions:** In women, CSC associated with subretinal precipitates, shorter duration, single occurrence, lack of HRT use, and absence of PED is more likely to resolve completely. CSC occurring in women over 50 or associated with PED formation is more likely to take longer to resolve.
Fluorescein angiography
1. Early phase of the angiogram shows hyper fluorescence corresponding to the size of the RPE detachment
2. In 95% of the cases one or as many as seven areas of leakage of dye are seen from the RPE into the sub retinal space.
3. Diffuses dye filling pattern - most common. The dye slowly to fill in the retinal detachment in 20 to 30 minutes.
4. Smokestack pattern – less common
5. In most of cases there is a single leak with the leaking site is within 1 disc diameter area of the fovea. But, the foveola is affected in less than 10% cases.
6. The incidence of leakage sites is greatest in the upper nasal quadrant, followed by lower nasal quadrant, and the lower temporal quadrant.
7. About 25% of the leaks are located in the papillomacular bundle.
Retrospective observational case series that reviewed the medical records and FA features of 229 consecutive patients with CSC between January 1999 and December 2001.

- 32% had symptoms in one eye and asymptomatic in the other eye but signs in both the eyes.
- 13% had bilateral symptomatic CSC
  - Overall bilateral involvement was found in 102 (44.54%) patients.
- Among the asymptomatic eyes, 62% had evidence of chronic subclinical CSC, whereas 39% had features of clinically healed CSC
- CSC developed in the asymptomatic eyes within 3 to 12 months in four of the 24 followed-up patients.

• Distribution of specific AF characteristics in acute and chronic-recurrent CSC.

- Autofluoresence
  - Acute CSC
    - N=39
  - Chronic-recurrent(n = 39)CSC
    - n=46

  - Normal: 8%(n = 3) vs. 4%(n = 2)
  - Decreased at leakage point: 72%(n = 28) vs. 76%(n = 35)
  - Increased at leakage point: 17%(n = 8)
  - Decreased elsewhere: 77%(n = 30)
  - Increased elsewhere: 85%(n = 39)
  - Summarized AF irregularities: 92%(n = 36) vs. 96%(n = 44)

Auto-fluorescence: Acute CSC

Pre-treatment

Post-treatment with thermal laser
Micropulse Laser
Micropulse Subthreshold Laser

Chronic CSC: Photodynamic Therapy

- Since 2003, there are reports demonstrating good results with use of photodynamic therapy (PDT) with verteporfin to treat chronic CSC
The mean choroidal thickness in the PDT group increased significantly from 389+/−106 mum at baseline to 462+/−124 mum (P = 0.008) by 2 days after treatment, and then reduced rapidly to 360+/−100 mum (P = 0.001) at 1 week and 330+/−103 mum (P<0.001) after 4 weeks as compared with baseline. Indocyanine green angiography showed decreased hyperpermeability in the PDT group after treatment.

Ophthalmology. 2010 May 14. [Epub ahead of print]
Subfoveal Choroidal Thickness after Treatment of Central Serous Chorioretinopathy.
Half Dose PDT for Chronic CSC

- 48 eyes of 48 patients with symptomatic chronic CSC underwent ICG angiography guided PDT with half dose (3 mg/m²) verteporfin.
- The mean CSC duration was 8.2 months (range, 3-40 months).
- At 12 months after PDT, the mean logMAR BCVA improved from 0.31 to 0.15 (P < 0.001)
- The mean improvement was 1.6 lines and 45 (95.8%) eyes had stable or improved vision
- Eyes without PED had significantly greater visual improvement compared with eyes with PED
- Patients with CSC of 6 months or less or younger than 45 years were more likely to gain vision by two or more lines after treatment
- 40 (83.3%) eyes had complete resolution of serous detachment at 3 months, with 43 (89.6%) eyes at 12 months.

Photodynamic therapy for acute central serous chorioretinopathy: the safe effective lowest dose of verteporfin.

Zhao MW, Zhou P, Xiao HX, Lv YS, Li CA, Liu GD, Li XX

30% of full dose is the lowest effective dose
Choroidal Thickness

- Enhanced depth imaging spectral-domain optical coherence tomography, which was obtained by positioning a spectral-domain optical coherence tomography device close enough to the eye to acquire an inverted image.
- Seven sections, each comprising 100 averaged scans, were obtained within a 5 degrees x 30 degrees rectangle to encompass the macula. The subfoveal choroidal thickness was measured from the outer border of the retinal pigment epithelium to the inner scleral border.
- The choroidal thickness measured in 28 eligible eyes of the 19 patients was 505 microm (standard deviation, 124 microm), which was significantly greater than the choroidal thickness in normal eyes (P < or = 0.001).
- Enhanced depth imaging spectral-domain optical coherence tomography demonstrated a very thick choroid in patients with central serous chorioretinopathy.
- This finding provides additional evidence that central serous chorioretinopathy may be caused by increased hydrostatic pressure in the choroid.

Autofluorescence: Acute CSC
Chronic CSC: Photodynamic Therapy

- Since 2003, there are reports demonstrating good results with use of photodynamic therapy (PDT) with verteporfin to treat chronic CSC.
- The mean choroidal thickness in the PDT group increased from 389 um at baseline to 462 um by 2 days after treatment, and then reduced to 360 um at 1 week and 330 um (P<0.001) after 4 weeks.
- Indocyanine green angiography showed decreased hyperpermeability in the PDT group after treatment.

Despite chronicity and recurrences seen in steroid associated CSC, serous retinal detachment resolved in all cases and modest improvement of visual acuity was observed following PDT at least for short term.

Given the difficulty of managing these cases, PDT as applied in this study may be an effective treatment.
Photodynamic Therapy for Steroid Associated Central Serous Chorioretinopathy

Tae-Gon Lee, MD and Judy E. Kim, MD
Since 2003, there are reports demonstrating good results with use of photodynamic therapy (PDT) with verteporfin to treat chronic CSC.

Ruiz-Moreno et al. treated 82 eyes in a multicenter study with a mean follow-up of 12 months using standard PDT parameter.

Subretinal fluid disappeared in all cases after PDT in chronic CSC without any cases of severe visual loss or complications.
Smokestack Leak on FA

- 14% of 479 consecutive cases had smokestack leak
- 70% occurred in first acute episode and 2.85% in chronic stage
- The median symptom duration was 15 +/- 34.28 days.
- 31% were in the parafoveal superonasal quadrant
- 94% was ascending type of leak
- In 2 eyes, more than one smokestack leak were seen within the same detached area

• Choroidal circulation develops a pool of extracellular fluid or edema
• This intrachoroidal edema or leakage exerts pressure on the pigment epithelium, causing it to blister–up into focal or multifocal PED
• PED disrupts or develops a mechanical opening, usually at the junction between its elevated and attached areas, permitting fluid to leak through resulting in the neurosensory detachment
When To Treat

- Good visual and anatomic results of treating acute CSC with half-dose verteporfin PDT in a randomized controlled clinical trial by Chan and colleagues (Ophthalmology 2008;115:1756-1765)
- Unless one needs faster visual recovery, recommend initial observation, since many resolve on their own
- However, best to treat before RPE changes or visual acuity loss occurs
Patients

- There were 6 male and 3 female patients with mean age of 53 years (range: 42-68 years)
- The need for corticosteroid included
  - Organ transplantation (3)
  - Chronic sinusitis (3)
  - Bronchial asthma (1)
  - Chronic dermatitis (1)
  - Systemic lupus erythematosus (1)
- The type of corticosteroid used included
  - Oral (4)
  - Nasal inhaler (4)
  - Topical (1)
A 43 year-old male patient with unilateral steroid associated chronic CSC who was treated with PDT using reduced fluence energy. The duration of CSC was 7 months and BCVA was 20/25 at baseline. OCT taken 12 months after PDT showed complete absorption of SRF and disappearance of PED. BCVA improved to 20/20.
Idiopathic Central Serous Chorioretinopathy
만성중심장액액막망막병증
(慢性中心腸液脈絡網膜膜病症)
CSC
Increased permeability from the choriocapillaris leads to focal or diffuse dysfunction of the retinal pigment epithelium causing a detachment of the neurosensory retina.

CSC has been described in patients with endogenously high levels of corticosteroids as well as in patients with hypercortisolism due to the treatment of ocular or systemic diseases.

[6] He suggested that angioneurotic patients were susceptible to retinal angiospasm and exudation in the macula.
Knowledge of the anatomy of the choriocapillaris-Bruch's membrane-RPE layer allowed ophthalmologists to surmise that there is a diffuse dysfunction of the RPE cells, the choroids, or both,\textsuperscript{[12]} regardless of the primary cause or the initiating event.
However, the cause of the choroidal abnormality is still unknown. The answer may lie in changes of the autoregulation in the choroidal blood flow.[12]

An alternative theory suggests that CSC results from dysfunction of the RPE (Figures 1a and b). This occurs following an undefined insult. It results in either a few impaired RPE cells or even a single RPE cell, which causes a reverse in fluid movement in a chorioretinal direction. This, in turn, leads to leakage of fluid in the subretinal space and finally to the development of a neurosensory retinal detachment.[12] Spitznas[64] suggested that focal damage to the RPE can reverse the direction of ion secretion and thus lead to greater fluid movement towards the retina than to the choroid.

Alternatively there could be a combination of increased fluid leakage from the choriocapillaris and impaired RPE function.[12] A persistent choriocapillaris abnormality could lead to prolonged stress of the RPE cells, which would not be able to pump in a retinochoroidal direction and therefore fluid would accumulate and cause a neurosensory detachment.
Experimental evidence to support the relationship of type A behaviour and CSC was provided by Yoshioka et al a few years before Yannuzzi's investigation. The authors 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.
Foveal attenuation, cystoid macular degeneration, and damage of the foveal photoreceptor layer cause visual loss in CSC.\cite{48, 100, 101} Cystoid macular degeneration, which is generally known as chronic macular oedema, was defined by Iida et al\cite{100} as cystoid spaces without intraretinal fluorescein leakage in the fovea.
One intriguing feature of CSC is the ability of photoreceptors to continue to function above a serous retinal detachement. This compares to the profound visual loss associated with rhegmatogenous retinal detachment. Experimental studies of retinal detachment have suggested that retinal detachment has a greater impact on cones than on rods.\cite{104,105} The OCT studies have confirmed that photoreceptor changes are more prominent at the fovea.\cite{101} However, the same authors observed that there was a much longer survival of photoreceptors in CSC. This, they explained on the basis of differences between the pathophysiological conditions underlying the neuroretinal damage in CSC patients and the behaviour of experimental animal models. Conversely, Chuang \textit{et al} \cite{106} suggested that rod dysfunction was more pronounced than cone dysfunction in CSC. Mori \textit{et al} \cite{107} declared that photopigment degeneration appears to take place in the rod photoreceptors of the detached retina. Wang \textit{et al} \cite{108} postulated that visual dysfunction should be more evident under scotopic conditions because the RPE visual cycle subserves predominantly the
Most clinicians would agree with the definition that Spaide et al.\textsuperscript{[114]} gave to chronic CSC, 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 FA. Polak et al.\textsuperscript{[36]} noted that the major distinction between chronic and acute disease is the fact that chronic disease has widespread pigment epithelial changes without overt detachment in most cases, whereas in acute disease there is focal pigment epithelial abnormality and marked detachment.
Attenuation of the foveal photoreceptor layer is associated with permanent visual loss as mentioned above. Imminent damage of foveal photoreceptors or foveal atrophy defined by the combination of chronic CSC signs with current activity involving or immediately threatening the fovea could be considered as the high-risk group for which treatment should be applied. Therefore, 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.
Before the development of other treatments, psychotherapy was suggested as a therapy.\cite{40} It was abandoned though as soon as there was progress in the understanding of the pathogenic nature of the disease. Corticosteroids were presented as the only treatment choice in CSC several years ago. They were administered subconjuctivally or systemically, but are no longer recommended as knowledge of CSC pathogenesis has evolved.\cite{119, 120, 121} Adrenocorticotropic hormone,\cite{119} anti-inflammatory drugs,\cite{122} retrobulbar tolazoline injections,\cite{123} subconjuctival injections of milk, albumin and salt solutions, anti-syphilitic and anti-tubercular drugs, insulin-free pancreatic extract, and thyroid extract have all also been suggested in the past.\cite{124} The use of the above agents was not proven to be effective by any clinical trials.\cite{2} The role of stimulation of adrenergic receptors in the pathogenesis of CSC led some investigators to suggest that β- or α-adrenergic blockade could be utilised in the treatment of CSC.\cite{41, 42} Their suggestions were based on small case series of patients and experimental models. However, there is no significant proof to support such a therapeutic approach. 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.\cite{43}
Corticosteroid Antagonists  Jampol et al.[81] first suggested that glucocorticosteroid antagonist activity may be of value in preventing or treating episodes of CSC. This was based on the association of endogenous hypercortisolism with the development of CSC.[39] The potential treatment of CSC episodes using antiglucocorticoid agents includes RU486 (mifepristone) and ketoconazole. RU486 is an active anti-glucocorticosteroid and anti-progesterone agent. This dual action results from similarities between receptors involved.[153] Its use in voluntary early pregnancy termination has delayed the initiation of ophthalmic clinical trials in the United States.

Ketoconazole is also an adrenocorticoid agent. It was first tested as a potential treatment for CSC by Golshahi et al.[58] in a prospective, case-controlled study. Patients received 200 mg of the drug per day for 4 weeks. The clinical benefit of this trial was not statistically significant. After 3 years, an increase in dosage of ketoconazole to 600 mg daily for 4 weeks was tried by Meyerle et al.[59] who found a delayed therapeutic response at 8 weeks after initiation of treatment. They postulated that their inconclusive results were because of short duration of treatment or/and normal baseline cortisol levels of the patients involved and they suggested larger, controlled trials to test the efficiency of ketoconazole in CSC patients.

Aspirin  Caccavale et al.[154] 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. They surmised that in all the 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.
STRESS

STRONG EMOTIONS
ANGER • FEAR • GUILT • SHAME • ANXIETY
Most of these are repressed and stored in the Subconscious Mind

Autonomic Nervous System Activates
The STRESS Response

Sympathetic Nervous System

HPA Axis

Symptoms of the Stress Response
Summary: Management of CSC

- For chronic or recurrent CSC, PDT is a treatment option.
- Reduced fluence PDT may be preferred in fovea involving cases.
- Further studies on best treatment parameters with PDT for CSC are still needed.
- Other treatment modalities are being investigated.
Summary: Management of CSC

• Question patients about medications
  • Steroids: all routes of drug delivery
  • Sympathomimetics: over the counter, recreational
• Advise patients with CSC to discontinue or lower the dosage of these medications
• Identify potential systemic risk factors for CSC
  • Cushing’s syndrome
  • Organ transplantation
  • Stress
This is particularly important, because pseudoephedrine and oxymetazoline are available as over-the-counter medications. Pseudoephedrine and MDMA are \( \alpha \)- and \( \beta \)-adrenergic receptors agonists, whereas oxymetazoline functions as an \( \alpha_1 \)- and partial \( \alpha_2 \)-adrenergic receptor agonist. Pseudoephedrine also induces the release of norepinephrine. Although the mechanism is unclear, an increase in choroidal blood flow