CENTRAL SEROUS CHORIORETINOPATHY

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All about the Eye

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Introduction

- Central serous chorioretinopathy (CSC) is one of several chorioretinal disorders characterized by serous detachment of the neurosensory retina and / or the retinal pigment epithelium (RPE).
- CSC is one of the most common diseases of the posterior segment of the eye and a frequent cause of mild to moderate visual impairment.

History

YEAR	AUTHORS	THEORY
1866	Von graefe	first described the disease as recurrent serous retinitis.
1916	Fuch	His work on the disease was appreciated and additional cases seen.
1927	Horniker	named disease as "Central Angiospastic Retinitis"
1930	Walsh & Sloane	"idiopathic flat detachment of macula"
1930	Gifford and Marquardt	Theory on Angioneurotic diathesis.
1953	Klien	theory on autonomic nervous system dysfunction.
1950's	Bennett & Maumenee	spectrum of macular disciform degeneration.
1955	Bennett	"central serous retinopathy"
1960's	Maumenee and Gass	FA appearance of CSC.
1967	Gass	"central serous choroidopathy"

Definition

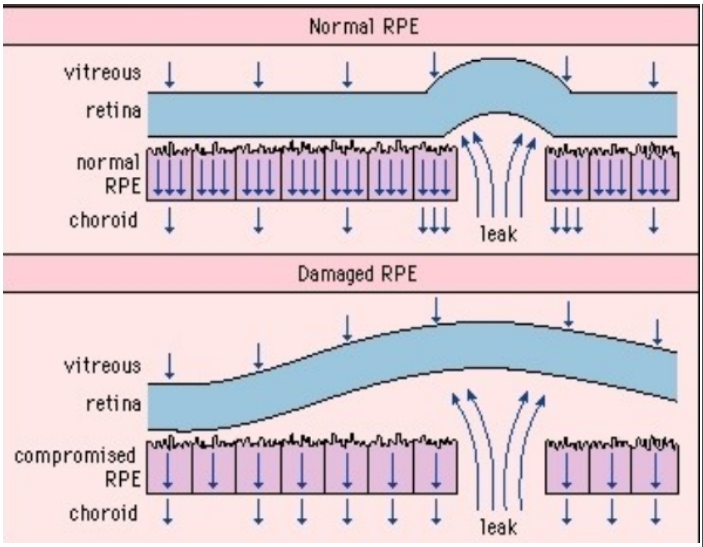
Active CSC is characterized by detachment of the neurosensory retina caused by accumulation of serous fluid between the photoreceptor outer segments and the RPE in combination with monofocal or multifocal changes in the RPE.

Pathogenesis

- The pathophysiology of CSC is still not completely understood.
- The widely fenestrated endothelium of the choriocapillaris allows leakage of small protein molecules and fluid into the intercellular space.
- But the RPE represents an impermeable barrier to the diffusion of fluid into the subretinal space.
- The RPE pump acts in a vitreous choriocapillaris direction to keep the subretinal space dry.
- The basis of the disease is diffuse dysfunction of the RPE cells, the choroid, or both.

RPE dysfunction theory

- The intact RPE creates a barrier between the neurosensory retina and choroid.
- In areas of chorioretinal scar tissue due to inflammation or photocoagulation, the pigment epithelial diffusion barrier remains permanently destroyed.
- Choroidal capillaries exert suction on the surrounding fluid.
- The intact RPE absorbs fluid in a retinochoroidal direction. Under certain condition, the function of the RPE is reversed, so it secretes in a chorioretinal direction.



RPE damaged via immunologic infections circulatory and neuronal mechanism

↓

RPE secretes ions in chorioretinal direction (towards retina)

↓

Choroidal fluid gets attracted into this area.

↓

Strong flow disrupts the diffusion barrier in this area.

Choroid dysfunction theory

Psychogenic, pregnancy, transplantation, type A, raised cortisol levels

↓

Adrenergic reaction causes damage to the choriocapillaries

↓

Hyperpermeability of choriocapillaries

↓

RPE cell degeneration

↓

Secondary changes in RPE causes leaks

↓

Serous retinal detachment

- The hydrostatic pressure of the fluid pooling under the detached RPE will then mechanically cause a discontinuity in the RPE layer with the subsequent leakage of fluid in the sub retinal space and neurosensory detachment of retina.

Types

- It is of 3 types :-

1. Typical or Classic CSC – Seen in younger patients & causes an acute localized detachment of retina with mild to moderate loss of visual acuity associated with one or few focal leaks seen during FFA.
2. Chronic CSC or Diffuse retinal pigment epitheliopathy – Wide spread alteration of pigmentation of the RPE related to the chronic presence of shallow subretinal fluid.
3. Atypical CSC – Bullous retinal detachments usually located inferiorly.

- Histologically CSCR (Spitnaz classification) has been classified as

Type 1—Detachment of sensory retina
Type 2—RPE detachment
Type 3—intermediate type—both sensory retina and RPE are elevated.

Demography

- **Age**: It affects young to middle aged individuals 20 – 45 years of age. In women age tends to be higher. In patients older than 50 years the ratio is changed to 2:1.
- **Sex**: Male predominance – 8 to 10:1
- **Race**: Commonly affects Whites, Hispanics, Asians – Japanese mostly. African- Americans are affected very less. Severe form occurs with - south east Asian and Latin origins.

Systemic associations of the disease

BOX 6-30-1 REPORTED RISK FACTORS AND ASSOCIATIONS WITH CENTRAL SEROUS CHORIORETINOPATHY

Systemic conditions	Medications
Type A personality	Corticosteroids
Emotional stress	Psychopharmacologic medications
Systemic hypertension	3, 4-methlyenedioxymethamphetamine
Gastroesophageal reflux disease	Antacids and antireflux medications
Pregnancy	Over-the-counter sympathomimetics
Organ transplantation	Antibiotics
Systemic lupus erythematosis	Antihistamines
Tobacco use	Sidenafil citrate
Alcohol use	
Membranoproliferative glomerulonephritis type II	
Helicobacter pylori infection	
Autoimmune disorders	

- Migraine like headache
- Hypochondrial behavior
- Hysteria
- Conversional neurosis
- Increased Cortisol levels in patients with Cushing's disease.
- Long term corticosteroid treatment in organ transplants & Respiratory allergies.
- The anti- inflammatory properties of steroids may cause delayed healing of the RPE defect.
- Cortisol, by suppressing synthesis of extracellular matrix components and inhibiting fibroblastic activity, also may damage directly the RPE cells or their tight junctions and may delay any reparative process in damaged RPE cells.

Symptoms

- Small PEDs may be present in macular or para-macular area before the onset of symptoms.
- This is followed by detachment of the neurosensory retina in the surrounding area.
- If detachment is not involving the central macula, the patient remains asymptomatic & detachment resolves spontaneously.
- If Neurosensory detachment involves the fovea-Symptomatic.

i. Metamorphopsia.- Amsler grid confirms metamorphopsia corresponding to the neurosensory detachment.
ii. Micropsia.
iii. Dyschromatopsia.
iv. Central scotoma (relative).
v. Loss of contrast sensitivity.

vi. Hyperopia – corresponding to anterograde displacement of fovea.
vii. Loss of dark adaptation

Differential diagnosis

Table 72.1 Important differential diagnoses of central serous chorioretinopathy and their differentiating features

Differential diagnosis	Differentiating features
Optic disc pit	Presence of optic disc pit, absence of leakage on FA
AMD	Older age group, CNV on FA
PCV	ICGA shows polyps and branching vascular network
Inflammatory and infectious diseases	Systemic features and bilateral involvement in VKH; ultrasonic T-sign in posterior scleritis
Autoimmune and vascular disorders	Systemic features are usually evident
Intraocular tumors	Ultrasound is useful in the detection and differentiation between different types of tumors

- POHS
- Sympathetic ophthalmitis
- Choroidal hemangioma
- Choroidal metastasis
- Leukemic infiltrates

Signs

- Usually a small hyperopic correction can be improved by refraction.
- AC and vitreous are normal.
- Fundus shows the following findings

1. **SEROUS RETINAL DETACHMENT**

- Round to oval well delineated shallow serous retinal detachment is present in the macula.
- This mildly darkened area is surrounded by a halo of light reflex and has an average size of 2 disc diameters.
- One or more discrete yellow to yellow grey, round to oval, well demarcated areas of detached RPE maybe observed.
- Loss of normal foveal reflex.

2. **SEROUS DETACHMENT OF RPE**

- These areas are often present under the superior half of the macular detachment when gravity forces the SR fluid inferiorly.
- These detachments often less than ¼ of disc diameter in size and have a grayish halo around them.
- Pigment changes maybe present on the detached surface and occasionally are seen only on an FA.

3. **SUB RETINAL PRECIPITATES**

- Multiple, variably sized yellow dot like precipitates caused by SR fluid turbidity maybe noticed at the level of the RPE.
- Diffuse gray, white SR deposits which may represent fibrin are occasionally present.
- Eventually the fibrin deposits dissolve by fibrinolysis and disappear.(There must be a significant hyperpermeability of the choriocapillaris to permit such a large molecule as fibrin (340,000 daltons) to exudate in the extravascular space)
- In a few cases the deposition of fibrin in the sub retinal space stimulates sub retinal fibrosis and fibrotic scar formation.
- This may cause permanent visual loss and may be complicated by sub retinal neovascularization or vascularization of the fibrous scar and RPE.
- In the fovea, a small yellow round spot maybe seen, which may be caused by increased xanthophyll visibility.

4. **EXTRA MACULAR ATROPHIC TRACTS**

- Gass described this as a pseudo-retinitis pigmentosa like atypical CSC presentation with prolonged and recurrent serous retinal detachment.
- Frequent in patients of Latin and Asian ancestry.
- Frequent recurrences, permanent visual loss and significant superior visual field loss are common.
- Yannuzzi et al stated severe or prolonged leakage of fluid or both from RPE defect in SR space at the posterior pole occurs in these patients.
- The SR fluid gravitates inferiorly to form a dependent neurosensory detachment as a flask, tear drop, dumb bell or hour glass pattern.
- The RPE under the chronic RD undergoes atrophic changes that appear as atrophic RPE tracts connecting the posterior pole with the dependant RD.
- Such RPE changes are better noted with FA
- Sometimes the tract of SR fluid connecting the macular detachment is so shallow that it is very difficult to appreciate even with the use of fundus contact lenses.

5. **MULTIPLE BULLOUS SEROUS RETINAL AND RPE DETACHMENT**

- Atypical presentation
- Healthy middle aged men
- Often RD associated with SR fibrinous exudates and multiple serous RPE detachment with areas of shifting SRF.

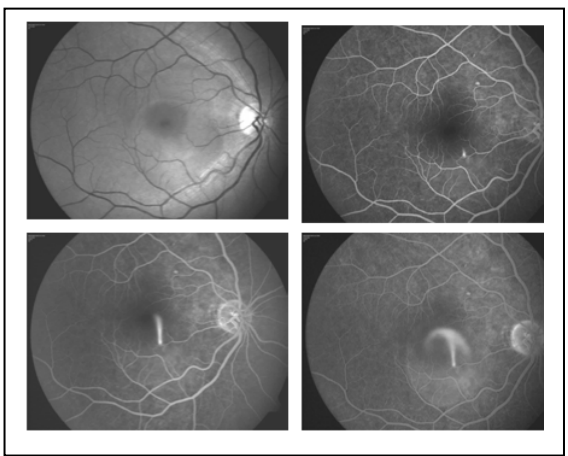
6. **RPE ATROPHIC CHANGES**

- Corresponds to previous CSC episodes.

Investigations

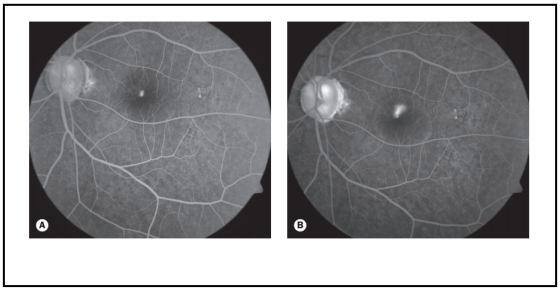
i. **FFA-** Two types of leakages are seen-

- **Smoke stack Pattern**.
- Seen in 7-20%
- Also known as ***mushroom or umbrella configuration***.
- The leakage first ascends superiorly and spreads laterally.



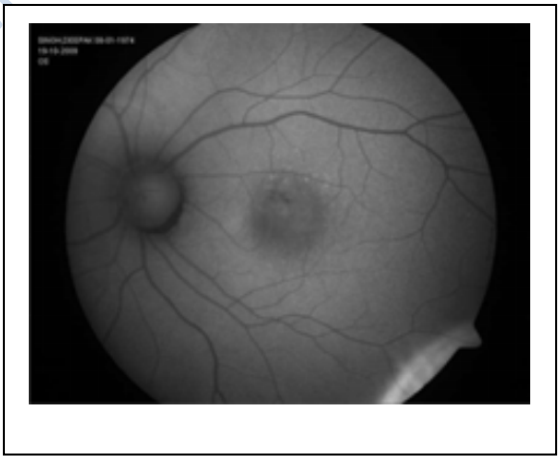
- It is unknown whether the flow is caused by a temperature gradient or by a density gradient existing between the Newly secreted fluid and surrounding fluid that has been

  in the subretinal cavity long enough to have cooled or to have become hyperdense because of preferential resorption of water and small solutes.
- Detachment associated with a smoke stack type of leakage is larger than that from an active pin point leakage.



- **Ink blot pattern**
- Most leakage points are with in 1 mm of fovea but can be till 3 mm of FAZ.
- In recurrent cases, leakage points is with in 1 mm of initial leakage points in 80% cases.
- Sometimes the RPED may be present superiorly than the SRD as the fluid collects inferiorly d/t gravity.
- EARLY PHASE—shows hyperfluorescent spot.
- LATE PHASE—spot gradually enlarges centrifugally until the area is filled with dye.

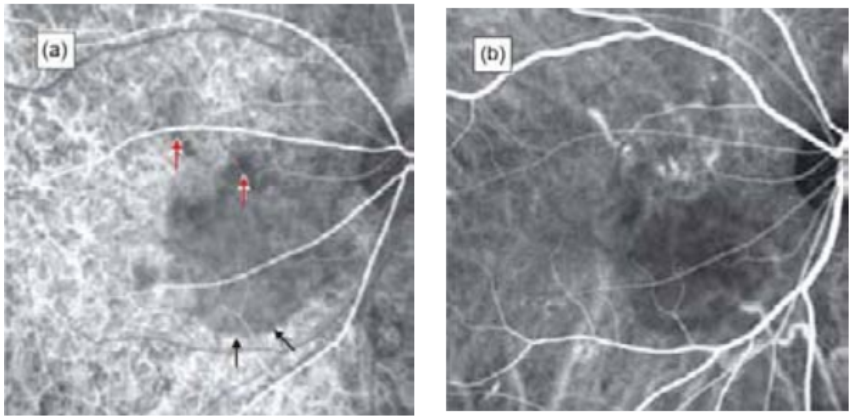
ii. **AUTOFLUORESCENCE PHOTOGRAPHY**



- In acute CSC, hypofluorescence has been demonstrated at the point of leakage
- Acute CSC that has persisted for some time often shows granular or semiconfluent hyperfluorescence throughout the area of detachment.
- In chronic CSC, irregular patterns of mixed hyper and hypofluorescence can be seen.
- After reattachment, the autofluorescent subretinal deposits disappear slowly over a period of several months.

iii. ICGA

- CSC are multi focal areas of hyperfluorescence in the early and midphases of the study, which then fade in the late phase of the study.
- These areas of hyperfluorescence are found in congruence with the leaking point seen with FA and fundus areas that appear clinically and angiographically normal and in normal fellow eyes of patients with CSC.
- These areas of early hyperfluorescence are believed to represent diffuse choroidal hyperpermeability.
- Multiple, “occult”, presumed RPE detachments that are imaged with ICGA but are not noted clinically or with FA.
- These areas represent the typical ICGA appearance of a serous PED, namely early hyperfluorescence and late hypofluorescence with a rim of hyperfluorescence.



- ICG of a patient with acute CSC the early frame- shows choroidal hypofluorescence corresponding to a two disk-diameter-wide area of serous detachment (inferior margin indicated by black arrows). Smaller areas of selective choroidal hypofluorescence near its upper border are marked using red arrows.
- During the angiographic mid-phase, these hypofluorescent areas demonstrate choroidal venous dilation and leakage at the locations in that correspond to the red arrows.

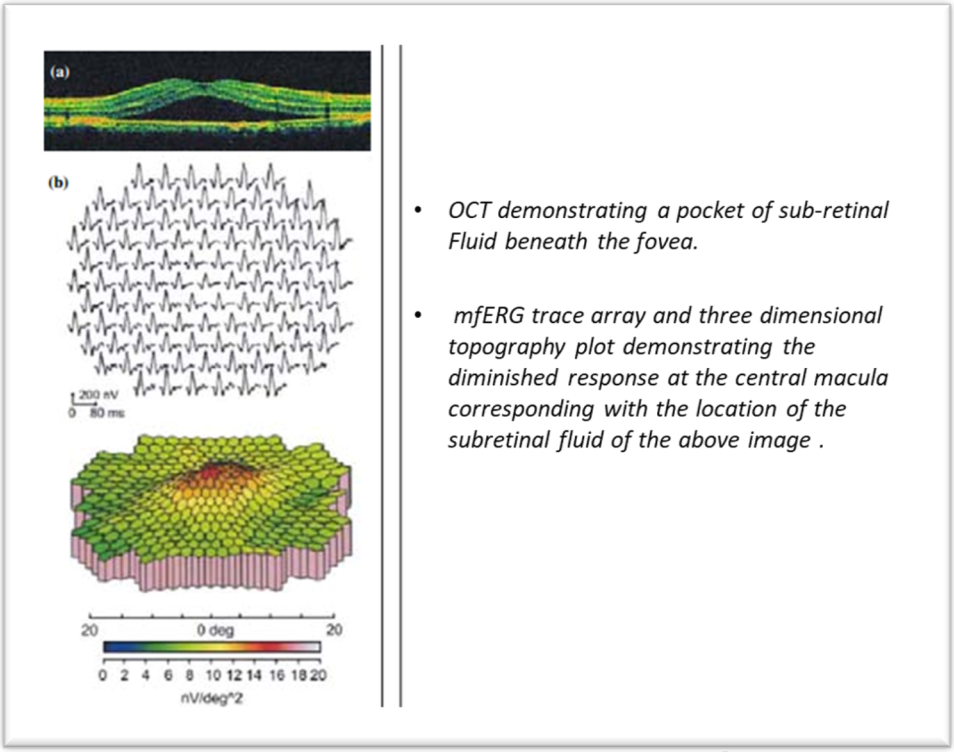
iv. **OCT**

- OCT reveals many aspects of pathophysiology of CSC, ranging from subretinal fluid, pigment epithelial detachments, & retinal atrophy following chronic disease.
- OCT is especially helpful in identifying subtle, even subclinical, neurosensory & macular detachments.
- OCT is also helpful in identifying the dreaded complication of CNVM in CSC
- OCT helps in evaluating the presence of shallow fluid in CSC as the volume of fluid may be of prognostic value as well as aid in patient education.
- Montero et al described Two patterns of OCT: -

a. An optically empty vaulted area of different heights under the neurosensory retina. Highly characteristic small bulges protruding from the RPE, angiographically related to leaking spots.
b. An almost semicircular space under the RPE, with thinner overlying retina.

v. **Multifocal Electroretinogram (mfERG)**

- It has been used to identify focal regions of decreased retinal function, even in asymptomatic or clinically inactive eyes.
- Lai et al, are using mfERG as a means of assessing the efficacy and safety of new treatment modalities for CSC.
- During acute CSC, retinal dysfunction is reflected by reduction in mfERG response amplitudes and delay in implicit times.
- With the use of mfERG, it has also been demonstrated that the fellow eye of patients with CSC may have abnormal mfERG responses.
- It has been shown that mfERG abnormalities may persist even after resolution of the subretinal fluid clinically.
- Thus, mfERG may therefore have a useful role in providing an objective measure of retinal function in research on the treatment for CSC.



- *OCT demonstrating a pocket of sub-retinal Fluid beneath the fovea.*
- *mfERG trace array and three dimensional topography plot demonstrating the diminished response at the central macula corresponding with the location of the subretinal fluid of the above image .*

vi. **MICROPERIMETRY**

- Microperimetry-1 (MP1, Nidek technologies, Italy) is an instrument for fundus-related perimetry.
- It captures fundus image of the patient's retina and at the same time projects light stimuli onto the retina.
- The patient's subjective response to each stimulus (seen/not seen) is recorded (functional information) together with the retinal location of the stimulus (anatomical information).
- The light stimuli size have been correlated to Goldmann stimuli sizes (Goldmann I-V) and the pattern are chosen by the operator and can therefore be adapted to different diseases of the macula.
- MP1 allows an accurate analysis of the central retinal function, combining a digital retinography, a computerized perimetry and a fixation assessment in one exam.
- It has shown that, despite clinical resolution of CSC, there is lower retinal sensitivity in the macula even once visual acuity returned to 20/20.
- The MP1 enables quantification of functional defects in patients with CSCR.

NATURAL HISTORY OF CSC

- If left untreated - CSC heals spontaneously within 12 weeks with full recovery of VA with scar formation.
- Recurrence in 1/2 to 1/3rd Patients.
- 3 or more recurrence seen in 10% patients.
- Recurrences are seen mostly with in 1 yr of disease but CSC may recur up to 10 yrs.
- Even a small single episode of CSC may be followed by chronic slowly progressive disturbances of RPE at post pole.
- Small percentage may develop CNV, perifoveal RPE atrophy or cystic macular degeneration with severe and irreversible loss of central vision.

- Patients with larger PEDS multiple recurrence, sub retinal fibrin deposits, multi focal leaks, dependent neurosensory detachment are at a greater risk of visual loss.

TREATMENT

- The high spontaneous remission rate favors conservative management.
- Lifestyle counselling & discontinuation of corticosteroids.
- If detachment persists for more than 3 months, photocoagulation or PDT should be considered.
- For treatment of the disease it is divided into 5 types: -

Acute	Conservative, counselling, if no resolution within 3 months of onset, consider focal photocoagulation/PDT
Recurrent- 2 or more episodes separated by >= 3 months	Photocoagulation if safe, otherwise PDT
Chronic	Photocoagulation if safe, otherwise PDT
Sequelae	None
Neovascularization	PDT &/or intravitreal Anti-VEGF

1. LASER PHOTOCOAGULATION

- Has been used for decades.
- Accelerates the resolution of the detachment.
- Also lowers the recurrence rate to about one fifth of what would be expected without active treatment.
- This beneficial effect of photocoagulation treatment can be explained as follows: -

i. The coagulation beam destroys the cluster of diseased RP cells, thus stopping the secretion of fluid beneath the neurosensory retina.

ii. The resulting scar helps to transport fluid back into the choriocapillaris.

- If leakage point is within 500 microns from the center of fovea, wait for 6 months before treating.
- Indications

i. Persistence of serous detachment for more than 3 months.

ii. Recurrences in eyes with visual deficit from previous episodes.

iii. Presence of permanent visual deficit from previous episodes in fellow eye.

iv. Development of chronic signs i.e, cystic changes in neurosensory retina or widespread RPE abnormalities.

v. Occupational or other patient needs that require prompt restoration of vision.

- Technique
- Strategy is to apply laser energy so as to obtain a confluent coagulation of moderate intensity covering the site of leakage responsible for the foveal detachment.
  - Spot size – 50- 200µ.
  - Exposure time – 0.1-0.2s.
  - Power- 80 MW titrated to 30 MW
  - End point – bleaching without whitening of outer retina.

- When multiple leaks are present, leakiest one should be treated first.
- Anatomic resolution of the macular detachment generally occurs in about 2 weeks in uncomplicated cases.
- But it may require up to 6 weeks in long-standing detachments with turbid sub retinal fluid.
- Complete visual recovery usually requires twice the amount of time.
- Complications

i. Worst is, inadvertent photocoagulation of the fovea.
ii. Persistent scotoma after treatment (should be told to the patient before giving treatment).
iii. Secondary CNVM.
iv. Progressive enlargement of the area of RPE atrophy.

2. PHOTODYNAMIC THERPY

- Indications: -

i. Juxtafoveal lesion.
ii. Subfoveal lesion.
iii. Lack of a clearly defined leakage hot spot.
iv. Concern about the potential induction of CNV.

- Mechanism

i. PDT works in CSCR by inducing choroidal hypoperfusion, vascular narrowing and remodeling to negate choroidal hyperpermeability which is consistently found in CSCR cases.
ii. PDT can also tighten the blood retina barrier.
iii. It works by photoradiation mechanism in which verteporfin is used as a photosensitizing agent followed by local application of light in the absorption spectrum of that agent (i.e. 689 nm).
iv. This will release free radicals that destroy endothelial cells causing closure of hyperproliferative vessels.
v. Reduced dose pdt- half dose of verteporforin, Reduced fluence- half power / time
vi. The use of half-dose verteporfin (3 mg/m2) or low fluence PDT (50% reduced light fluence) is done as a precaution against permanent RPE or choriocapillaries damage.
vii. A dose of 50 J/cm2 (full-fluence PDT), or 25 J/cm2 (half-fluence PDT).
viii. Fifteen minutes after intravenous infusion, low power laser is applied (standard dose of 50 J/cm2, irradiance of 600 mW/cm2 of 689 nm light over 83 seconds

3. TRANSPUPILLARY THERMOTHERAPY

- Transpupillary thermotherapy (TTT) is a 810 nm long-pulse low-energy IR diode laser.
- It works by raising the temperature of the choroid and outer retina while sparing the inner retina and photoreceptors to some degree, but the exact mechanism is not clear.
- More well-structured RCTs with long-term results are required to establish the role of TTT in the treatment of CSCR.
- TTT involves long exposures (~60 s) of a large spot (1.2–3 mm) at low irradiance (~10 W/cm2), using a near-infrared Diode (810 nm) laser that will induce intralesional hyperthermia and subsequent vascular occlusion and lesion shrinkage. POWER 200-600mW

	PDT	TTT	Conventional laser
Wavelength used	Diode red 689 nm	Diode infrared 810nm	Green, red, infrared, etc. 514-810nm
Pulse duration	83 seconds	60 seconds	Few hundred microseconds
Temperature rise	2 degree C	10 degree C	42 degree C

4. MICROPULSE DIODE LASER PHOTOCOAGULATION

- This method of treatment uses subthreshold diode laser energy in order to minimize retinal damage.
- It is effective in CSCR with point source leakage but not in eyes with diffuse leakage, and leaves no clinically detectable laser-induced damage.
- Since there is no visible endpoint to diode micropulse laser (DMPL) application, ICG enhanced DMPL can be used to identify treated areas with post-treatment ICG angiography as they appear darker.
- Micropulse system, the ‘‘on’’ time (typically 100μs to 300μs) is the duration of each micropulse and the ‘‘off’’ time (generally 1,700μs to 1,900μs) is the interval between consecutive micropulses. Short “on” times that limit thermal elevation and long “off” times that allow for heat dissipation decrease collateral damage to the retina and prevents coagulative necrosis.

5. INTRAVITREAL ANTIVASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF)

- Attempts to treat acute and chronic CSCR with intravitreal bevacizumab are based on the hypothesis that choroidal hyperpermeability is associated with increased expression of VEGF.
- Anti-VEGF therapy has a much obvious, well-established role in CNVMs secondary to CSCR.

6. CARBONIC ANHYDRASE INHIBITORS

- Systemic acetazolamide promotes the resorption of SRF.
- However, there is no evidence that treatment promotes healing of the RPE lesion, long-term preservation of visual function, or a reduced rate of recurrence.

7. NEW THERAPIES

- Adrenergic blockers – metoprolol- As CSCR is closely associated with type A personality which is characterized by high adrenergic activity, blocking adrenergic receptors might have a positive effect on CSCR.
- Aspirin- CSCR is due to impaired fibrinolysis and increased platelet aggregation in the choriocapillaris.it is presumed that aspirin works in such cases through its fibrinolytic and anti-platelet action
- Helicobacter pylori treatment
- Methotrexate
- Several systemic drugs have been variably reported to be effective in resolving cases of chronic, recurrent, or resistant CSC; medications include
- Mifepristone- Its mechanism of action in cscr is mediated through its glucocorticoid and progesterone receptor antagonistic effects

- Finasteride - is a weak anti-androgen
- Ketoconazole- Ketoconazole has anti-glucocorticoid effects by blocking the conversion of cholesterol to androgenic glucocorticoid end-products
- Spironolactone & Eplerenone - both aldosterone antagonist agents. Spironolactone possesses additional anti-androgen properties.
- Rifampicin- is an anti-tuberculous medication which is thought to facilitate catabolism of endogenous steroids.
- Valproic acid - The rationale for their use rests largely on their impact on steroid metabolism.

SEQUELAE

Subretinal Fibrosis	Subretinal lipid deposition
Fibrotic scar especially with treatment with steroids	Peripheral dependent bullous neurosensory detachment
Cystoid retinal changes in detached area	CME
Retinal pigment atrophic tracts	Choriocapillary atrophy
Pigment migration atrophy	CNVM
RPE tear	