

## Exogenous and endogenous corticosteroids and their link to Central Serous Chorioretinopathy

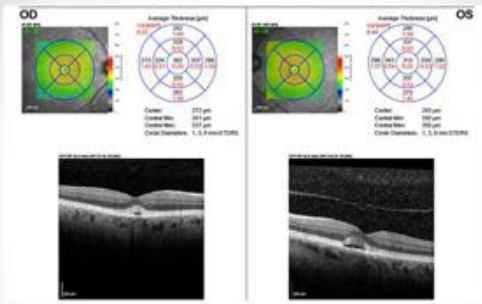
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## Objectives

- By the end of the presentation, attendees will be able to
  - Recognize the association between corticosteroids and central serous chorioretinopathy
  - Identify factors that aid corticosteroid absorption
  - Recognize the role of hypothalamus-pituitary-adrenal axis and sympathetic nervous system in stress response
  - Recognize the role of elevated plasma cortisol in CSC
  - Discuss the role of choroid and RPE in the development of CSC

## Patient JM – 70 y.o. male

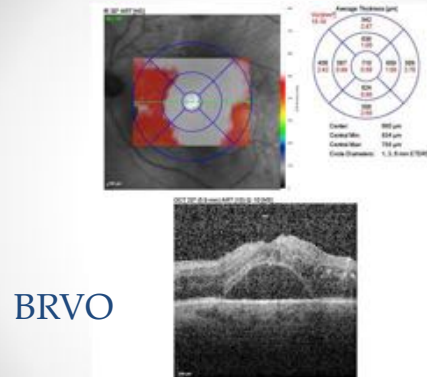
- CC: Seeing a crescent shape in right eye for 10 days.
- Uncorrected VA: 20/20<sup>-2</sup> OD and 20/25<sup>-2</sup> OS
- PERRL (-)APD
- FTFC OD and OS
- IOP: 12/10 mmHg
- Lens: clear PCIOL OU, slight sup displacement OD
- Vitreous: PVD OU
- C/D: 0.35r OD and 0.40r OS
- Macula:
  - OD: small (<1/4DD) area of elevation centrally OD;
  - OS: larger area of elevation with pigment changes centrally;
- Vessels: normal
- Periphery: intact



Bilateral Central Serous Chorioretinopathy.

## Differential diagnoses<sup>5,6</sup>

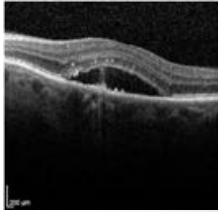
- DME
- ARMD
- BRVO
- CRVO
- Hypotony maculopathy
- Retinal vasculitis
- Retinal macroaneurysm
- Ocular histoplasmosis
- Polypoidal choroidal vasculopathy
- Optic nerve pit
- Idiopathic uveal effusion syndrome
- Posterior scleritis



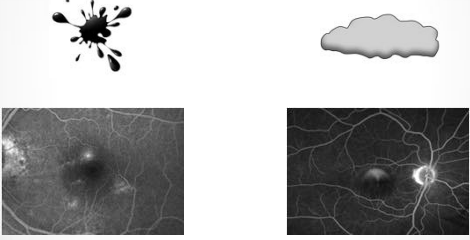
BRVO

## CSC overview

- **Fourth** most common retinopathy<sup>1</sup>
  - After ARMD, diabetic retinopathy, vein occlusions
- **Anatomy**
  - **Serous** retinal detachment
  - Fluid leakage at the level of RPE
    - Single or multiple
    - **Inkblot vs. smoke stack**



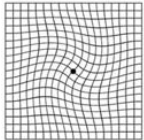
## Fluorescein Angiography



<http://www.premmedica.com/images/cv2.gif>

## CSC overview

- **Healthy males**
  - 9.9 in 100,000 men and 1.7 in 100,000 women<sup>3</sup>
  - 6:1 M:F ratio<sup>54</sup>
  - 20-30% recurrence<sup>29,54</sup>
  - Good health, no mental illness, socially integrated<sup>56</sup>
- **Symptoms**
  - Asymptomatic
  - Decreased visual acuity
    - 20/20 - 20/200
  - Decreased contrast sensitivity
    - Stays reduced even after resolution<sup>58</sup>
  - Metamorphopsia
    - Amsler grid abnormalities in 40% after resolution
  - Dyschromatopsia
    - Tritan axis<sup>57</sup>
  - Positive scotoma



## CSC overview

Acute	Chronic
<ul style="list-style-type: none"> <li>• Resolves spontaneously in 2-3 months<sup>53</sup></li> <li>• 95% of cases</li> <li>• Visual prognosis depends on presenting acuity</li> <li>• 15-50% recurrence<sup>53</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Typically lasts over 6 months</li> <li>• 5% of cases<sup>58</sup></li> <li>• Diffuse RPE abnormalities</li> <li>• Older population</li> <li>• More significant reduction in visual acuity</li> </ul>

- Risk of developing CNV after CSC is 0.3-2.0% per year

## CSC risk factors

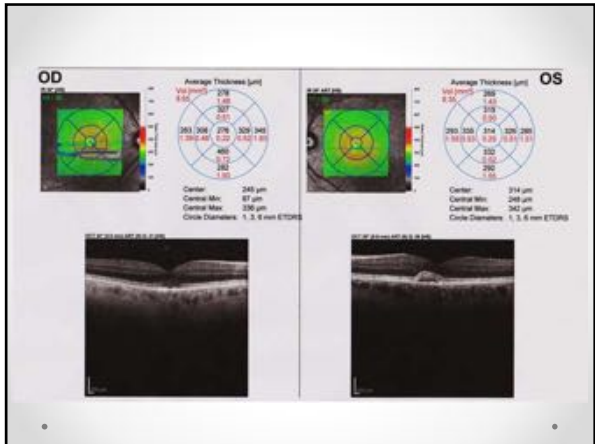
- Pregnancy<sup>7</sup>
- Obstructive sleep apnea
- HTN<sup>10</sup>
- Collagen Vascular Disease<sup>53</sup>
- Psychopharmacologic medication use<sup>10</sup>
- Helicobacter pylori<sup>53</sup>
- Allergic respiratory disease<sup>53</sup>
- Cushing's syndrome<sup>53</sup>
- **Type A personality**<sup>11</sup>
- **Psychological stress**<sup>8</sup>
  - Divorce, bankruptcy, critical illness, poor coping mechanisms
  - Acute stressor precedes onset by a week on average
- **Corticosteroid use**<sup>7</sup>

## Medications

- Adalimumab inj pen kit
- Albuterol/ipratropium inhaler
- Ammonium Lactate cream
- Balsalazide Disodium
- Betamethasone Valerate 0.1% cream
- Clobetasol Propionate 0.05% ointment
- Hydroxyzine Pamoate
- Mometasone Furoate 220mcg inhaler
- Omeprazole
- Polyethylene Glycol
- Pravastatin
- Sodium Fluoride oral cream
- Triamcinolone 0.1% cream
- Venlafaxine
- Aspirin 81mg
- Nefazodone

## 2-month follow-up

- CC: visual phenomenon still present, but decreasing in intensity. Still taking steroid creams and inhaler.
- VA: 20/20 OD and OS
- PERRL (-)APD
- IOP: 14/13 mmHg
- Posterior segment same OU
  - Except flat macular appearance OU



## Glucocorticoids and CSC

- No data to estimate prevalence of CSC in patients on treatment with glucocorticoids
- About 3.3%-9.1% of CSC patients were on steroids<sup>10,26</sup>
- Over 200 cases reported in literature of CSC during glucocorticoid therapy:<sup>9</sup>
  - Oral routes
    - Intravenous
    - Intramuscular
    - Epidural
    - Inhaled
    - Intranasal
    - Topical skin applications
    - Combination of two modes
- Interestingly ocular steroids not so much (topical or intravitreal)

## Steroid-associated CSC

- Older age<sup>9</sup>
- More bilateral and chronic
  - Bilaterality in woman 23% vs 11%<sup>27</sup>
  - 33% in exogenous vs. 20% in all<sup>28,29</sup>
- Male:Female ratio more equal
  - 3:1 vs 8:1<sup>9</sup>
  - Woman who develop CSC are more likely than men to use steroids<sup>10,26,27</sup>
- Wide range of dosages and treatment durations
  - 10-15mg per day to 1 g IV per day<sup>9</sup>
  - Few days to few years
- Other considerations
  - Diseases treated with corticosteroids
  - Catecholamines<sup>23,24</sup>
  - Testosterone<sup>25</sup>

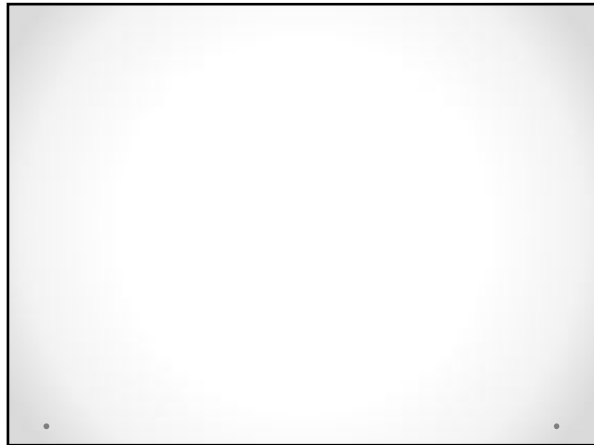
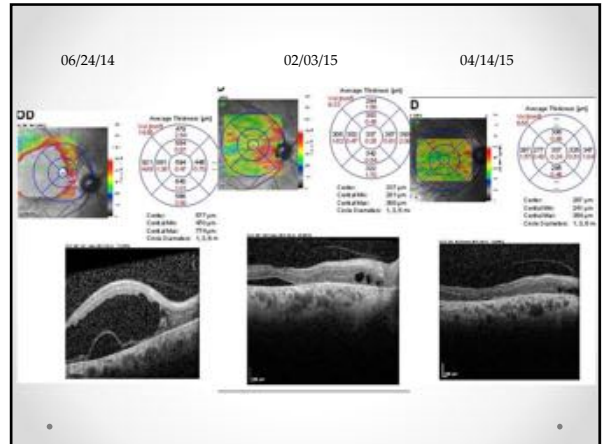
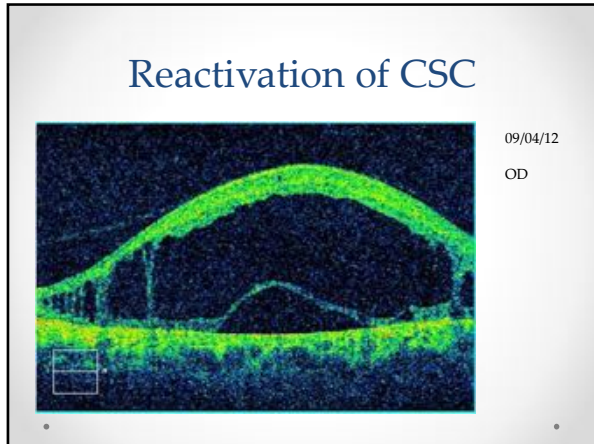
## CSC from topical dermal steroids

- 43 yo F from mometasone furoate 1% cream for lichen planus in arms – did not discontinue, focal laser tx at 7 months without complete resolution, but improved acuity<sup>13</sup>
- 47 yo F used steroid cream (unknown) for psoriasis (last administration coincided with start of symptoms), resolved at 9 months even with intermittent continued steroid cream use<sup>14</sup>
- 25 yo M used calcipotriene 0.005% cream for psoriasis for 16 months, discontinued, condition resolved in 3-4 months<sup>12</sup>
- 32 yo M used 1% hydrocortisone acetate cream for facial seborrheic dermatitis<sup>15</sup>
- 37 yo M using diflucortolone valerate 0.1% cream for pityriasis versicolor<sup>15</sup>

## Main factors in drug absorption

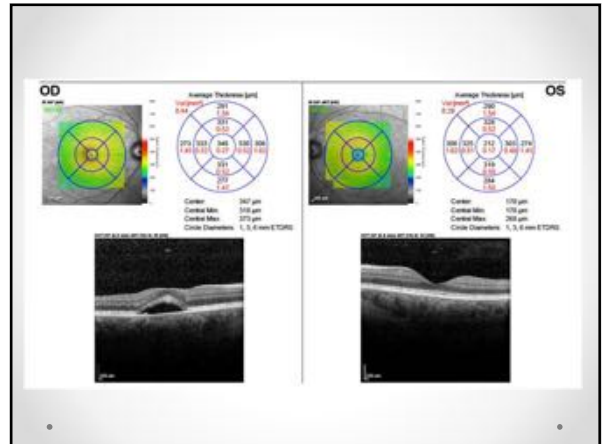
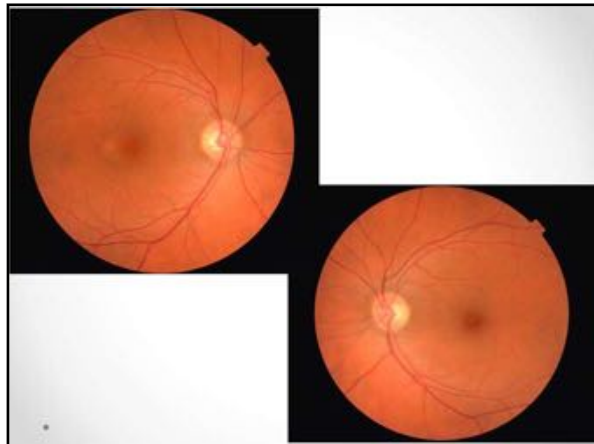
- Strength/potency of steroid
- Length/frequency of application
- Nature of skin problem
- Site treated<sup>13</sup>
  - Forearms: 1%
  - Arms: 4%
  - Face: 7%
  - Eyelids and genitalia: 30%
  - Palm: 0.1%
  - Sole: 0.05%





### Patient LS – 39 y.o. female

- CC: Can't see soccer ball when watching games on TV.
- History of burned left eyeball with a curling iron at 12 yo
- VA: **20/20 OD and OS** with strain
- PERRL (-)APD; full motilities OU; visual fields FTFC OU
- Manifest refraction: **+0.25 sph OU**
- Unremarkable anterior segment
- IOP: 10/09 with Tonopen
- Lens: Clear OU
- Vitreous: Clear OU
- C/D: 0.4r OU; **temporal pallor OU**
- Macula: **1 DD area of elevation OD**, with hypopigmentation; OS: flat, dry (+)FLR
- Vessels: normal OU
- Periphery: intact OU

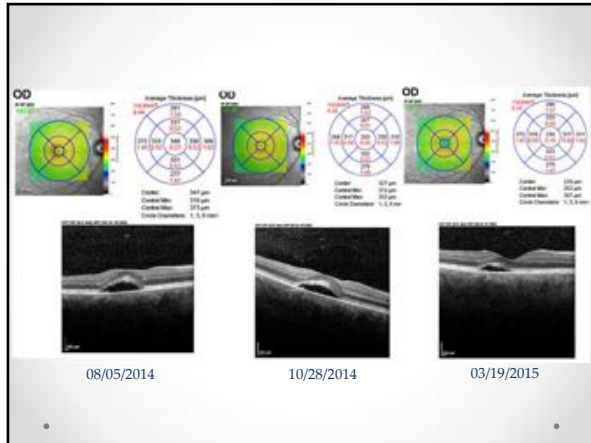


## Pertinent Medical History

- H/o attempted suicide 2 weeks prior
- Anxiety
- Insomnia
- History of alcoholism
- Anorexia
- Bulimia Nervosa
- Major depression
- Eating disorder

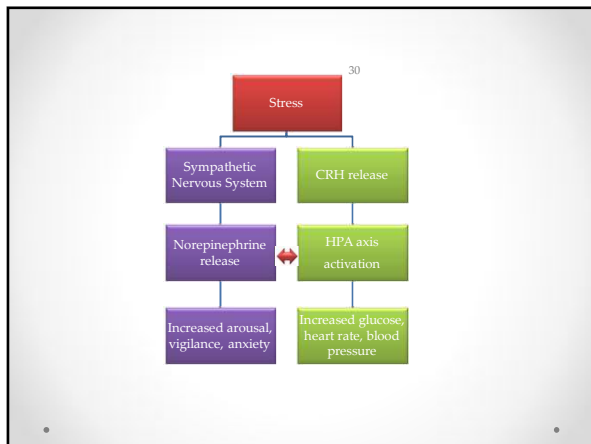
## Diagnosis

- 1. Idiopathic central serous retinopathy, OD. Patient unaware of onset.
  - 2. Possible mild nutritional optic neuropathy OU.
  - 3. Presbyopia OU.
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- 1. Patient education. Monitor in 2 months.
  - 2. Ordered serum B-12. Thorough education on nutrition, alcohol consumption. Consider VF testing.
  - 3. +1.25 sph reading glasses recommended.



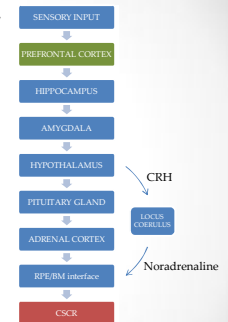
## The role of stress

- Type A behavior <sup>11</sup>
  - Competitive drive
  - Sense of urgency
  - Aggressive nature
  - Hostile temperament
- Type A vs. Type B
  - 60% of CSC patients have Type A behavior
  - Patient with CSC is 3.4x more likely to be Type A than Type B
- People with Type A show increased sympathetic activity in response to challenging situations, as compared to Type B
  - Skin temperature <sup>41</sup>
  - Muscle vasodilation <sup>44</sup>
  - Pupillary dilation <sup>45</sup>
  - Pulse rate <sup>41</sup>
  - Blood pressure <sup>42</sup>
  - Plasma catecholamines <sup>43,45</sup>
  - Plasma cortisol <sup>44</sup>
- Type A students produced 40x more cortisol and 4x more epinephrine than Type B students <sup>46</sup>



## Prefrontal cortex<sup>47</sup>

- Does not fully develop until 25 y.o.
- No neural element in stress response
- No CSCR in kids



## Adaptation during stress<sup>30</sup>

Behavioral Adaptation

- Acute facilitation of adaptive and inhibition of non-adaptive neural pathways
- Increased arousal, alertness
- Increased cognition, vigilance, and focused attention
- Suppression of feeding behavior
- Suppression of reproductive behavior
- Containment of stress response

Physical Adaptation

- Oxygen and nutrients directed to the CNS and stressed body site
- Altered cardiovascular tone, increased blood pressure and heart rate
- Increased respiratory rate
- Increased gluconeogenesis and lipolysis
- Detoxification from toxic products
- Inhibition of growth and reproductive systems
- Containment of stress response
- Containment of inflammatory/immune response

## Chronicity of stress response

- Stress response is meant to be of limited duration
  - Anti-anabolic, catabolic, immunosuppressive effects
- One-time CSC in over 50%
  - Adaptation by anticipatory response<sup>47</sup>
  - Learning predictive cues
  - Increased glucocorticoids after acute stress, but decreased after chronic intermittent stress<sup>48,49</sup>
- Chronic stress response results in severe chronic disease<sup>30</sup>
  - Failure of adequate counterregulation
  - Limited adaptation becomes prolonged maladaptation

## Maladaptive stress response. AKA - Melancholic depression.

+

Arousal

Vigilance

Cognition

Assertiveness

Decreased emphasis on feeding and reproduction

Anxiety

Hypervigilance, insomnia

Focus on depressive ideas

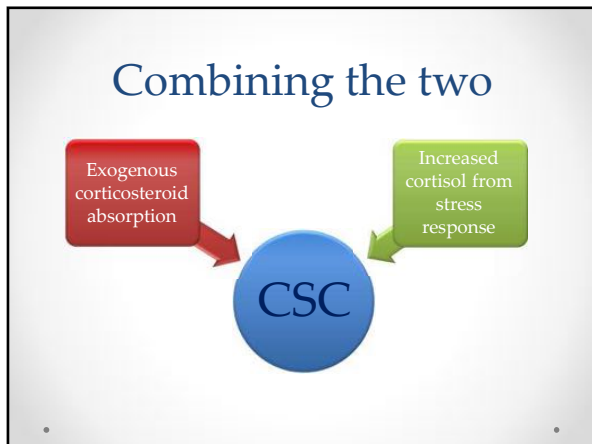
Excessive cautiousness

Anorexia, decreased libido

-

## Disorders associated with dysregulation of the stress system<sup>30</sup>

Increased Stress System Activity	Decreased Stress System Activity
<ul style="list-style-type: none"> <li>• Severe chronic disease</li> <li>• Anorexia nervosa</li> <li>• Melancholic depression</li> <li>• Panic disorder</li> <li>• Obsessive-compulsive disorder</li> <li>• Chronic active alcoholism</li> <li>• Alcohol and narcotic withdrawal</li> <li>• Chronic excessive exercise</li> <li>• Malnutrition</li> <li>• Hyperthyroidism</li> <li>• Premenstrual tension syndrome</li> <li>• Vulnerability to addiction</li> </ul>	<ul style="list-style-type: none"> <li>• Atypical depression</li> <li>• Cushing's syndrome</li> <li>• Seasonal depression</li> <li>• Chronic fatigue syndrome</li> <li>• Hypothyroidism</li> <li>• Obesity</li> <li>• Posttraumatic stress disorder</li> <li>• Nicotine withdrawal</li> <li>• Vulnerability to inflammatory disease</li> </ul>



## Role of the RPE

- Defect in RPE
- Focal defects promote flow into choroid<sup>38</sup>
- Steroids can modify electrophysiological parameters, influencing fluid transport<sup>32</sup>
- Steroids enhance blood-brain barrier by strengthening tight junctions<sup>33</sup>
- Perhaps, increased tissue hydrostatic pressure in the choroid along with focal loss of RPE polarity can result in fluid penetration into subretinal space.

## Role of the choroid

- Choroidal hyperpermeability
- Choroidal thickness measurements
  - Thicker in eyes with CSC<sup>35</sup>
  - Thicker in fellow eyes if choroidal hyperpermeability is present<sup>34</sup>
- Corticosteroids and the regulation of blood flow
  - Inhibition of nitric oxide production<sup>37,40</sup>
  - Hypercoagulability and augmented platelet aggregation<sup>50</sup>
    - Increased blood viscosity, increased vascular resistance, increased endothelial pressure
  - Choroidal blood flow elevation<sup>52</sup>
    - Inverse correlation between visual recovery and choroidal blood flow velocity
    - Laser interferometry vs. laser speckle flowgraphy vs. laser doppler flowmetry
  - Cadherin 5 and genetic variation<sup>51</sup>
    - cell-cell adhesion molecule in vascular endothelium downregulated by steroids

## Treatments

- Observation – fair
- Discontinuation of steroids – good
- Laser Photocoagulation – good
- Photodynamic therapy – good
- Anti-glucocorticosteroids – poor
- CAls – poor
- Anti-VEGF - poor
- Aspirin – poor
- Diode Micropulse laser – poor
- Transpupillary thermotherapy – poor
- Beta-blockers to prevent recurrence - poor
  - Due to stress



## Final thoughts...

- "...disorder is not caused by a solitary etiologic factor producing a specific constellation of macular manifestations. Rather, its pathogenesis is more likely related to the interrelationship between finely balanced components of a complex biopsychological system involving a person's genetic endowment, environment, and behavioral pattern."<sup>11</sup>

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