Update On Central Serous Chorioretinopathy

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• Will be discussing the off label use of bromfenac, nepafenac, eplerenone, rifampin, and photodynamic therapy

Update on Central Serous Chorioretinopathy

- Explain the newer diagnostic technologies
- Discuss the most recent data on newer treatments

History

- 1886 - Recurrent Central Retinitis - Von Graefe
- 1955 - Central Serous Retinopathy - Bennet and Maumenee
- 1965 - Central Serous Chorioretinopathy - Gass
- Diffuse retinal pigment epitheliopathy or Chronic CSC.
**Epidemiology/Demographics**

- High percentage of men (72%-88%)
- Males (8-9 to 1)
- No upper age limit
- No cases reported under the age of 20
- Peak prevalence 45 yrs - higher in chronic and female patients.
- Bilateral involvement in 40%
- CSC in older patients more common than you think
  - Spaide found 130 patients with neurosensory detachments – 57 were diagnosed with CSC

**Classification**

- Two types
  - Younger patients
    - Bullous focal retinal detachment
    - Little fundus change and only mild visual change
    - Few areas of hyperfluorescence
  - Older patients
    - Shallow fluid
    - Widespread RPE change
    - Diffuse retinal pigment epithelialopathy
    - Associated with chronic steroid use

**Pathogenesis**

- Unknown
- Theories
  - Defect in the tight junction of RPE cells
  - Polarity of the pump is changed
  - Choroidal vascular hyperpermeability

**Choroidal vascular hyperpermeability**

Initially there is choroidal hyperpermeability with congestion of the choriocapillaris along with exudation of protein and fluid.
Choroidal vascular hyperpermeability

Retinal pigment epithelium (RPE) pump decompensation occurs over time with the formation of a pigment epithelial detachment.

Eventually, RPE defect develops, leading to leakage into the subretinal space.

This leads to elevation of the neurosensory retina and a neurosensory retinal detachment.

Diagnostic Testing

- Angiography – Fluorescein and Indocyanine
- Fundus Autofluorescence (FAF)
- Spectral Domain OCT (SDOCT)
Fluorescein Angiography

- Most common - pinpoint hyperfluorescence areas
- Fills sensory detachment, but slow
- Areas of leakage usually hypopigmented
- Smokestack 7-25%
- Most common area of leakage is superonasal macula 0.5 - 1.5 mm from the foveola

ICG

- Hot spots

Autofluorescence

- Autofluorescence is a rapid non-contact, non-invasive way to evaluate RPE function.
- AF can evaluate the amount of lipofuscin that is accumulated in retinal pigment epithelium.
- By evaluating fundus autofluorescence images and thus lipofuscin accumulation, disturbances within the RPE can be readily detected.
- Helps explain to the patient why their vision isn’t good

AF and CSR

- Acute CSC - hypofluorescence at leakage site
- Middle to late CSC - granular or semi-confluent hyperfluorescence
- Chronic CSC - irregular patterns of mixed hyper and hypofluorescence can be seen.
**FAF and CSR**

- **Acute CSC** - hypofluorescence at leakage site
- **Middle to late CSC** - granular or semi-confluent hyperfluorescence
- **Chronic CSC** - irregular patterns of mixed hyper and hypofluorescence can be seen.

**Wide Field FAF in CSR**

- Are there abnormalities in FAF in the mid and far periphery?
- Sadda et al 2012
  - Yes – 53% have abnormalities

**OCT**

- Shallow serous detachments
- Subretinal and sub RPE fluid are both possible - rule out CNV
- Late chronic disease can show cystoid edema
**Choroidal OCT Imaging**

- Association between choroidal thickness and CSR
- Study by Duker and colleagues identified 23 patients with atypical CSR versus age matched control patients

**What is the best way to measure choroidal thickness?**

- Currently not automated and no controls to show whether the reading is abnormal
- Obtain an EDI protocol scan
- Manual caliper measurements from the fovea

**What is the best way to measure choroidal thickness?**

- Good rule of thumb: Subfoveal retina should be as thick as the subfoveal choroid
- Minor fluctuations of 20-30 microns considered normal
- Make sure to take into account myopic status
  - >6D myopia = CT avg is 98 microns
  - Every 1 D of myopia – 8.7 microns of decreased thickness

**Treatments**

- Acute
- Chronic – defined as the presence of subretinal fluid for greater than 4 months without improvement
**Acute: Natural History**

- Most resolve within 3 months
- 1/3-1/2 reoccur
- Less than 10% greater than 3 times
- Can consider laser/PDT with need for acute vision
- NSAIDs may hasten recovery

**Non Steroidal Anti-Inflammatory Drugs**

- Work well in Cystoid Macular Edema
- Studies also done in AMD and DME
- Different mechanism of action than Corticosteroids
- Block Cox 1 and Cox 2 cycles
- Studies have shown that NSAID decrease cortisol levels during stress vs controls in both and animals


**Purpose**

- To determine if the addition of topical NSAID medication (Bromfenac or Nepafenac) can decrease the time to resolution of edema and restoration of vision in patients with acute central serous Choroidopathy if dosed at high doses (QID) over an extended period of time.

**Control Data vs Combined Data**

- **Control Data: Charlotte and Cole**
  - N= 49 patients
  - Mean 129 days combined
  - Range 12-362 days
  - Difference is significant (p< 0.0002)

- **Treated Group: MCOA (define)**
  - N = 38 patients
  - Mean 42 days
  - Range: 14-96 days
  - Difference is significant (p< 0.0002)
Mean time to resolution of OCT

- Mean time to resolution of OCT
  - 80 days in Control
  - 44 days Bromfenac
  - 44 days Nepafenac
  - Control vs treated (p=0.002)
  - There was no statistical significance between Bromfenac and Nepafenac, but each of them were statistically superior to control.

Chronic CSR Treatment modalities

- Anti-VEGF treatment (Bevacizumab)
  - Case reports have shown variable results, some beneficial and some showed no beneficial effect
- Finasteride – an inhibitor of dihydrotestosterone synthesis
  - Positive response in small case series of chronic CSC patients, but with recurrent exudation after discontinuation
- Acetylsalicylic acid (aspirin) – anti-inflammatory and antiplatelet effects that may counteract choroidal vascular congestion, ischemia, and inflammation in CSC
  - Benefits shown in one study, optimal dose of 75-100 mg

- Rifampin – increases the metabolism of endogenous steroids
  - Successful treatment in small case series of patients treated with 300 mg 2x daily
- Mifepristone – an antagonist of glucocorticoids and progesterone receptors, inhibits cortisol-induced peripheral vasoconstriction
  - Treatment response seen in 16 patients with chronic CSC treated with 200 mg daily for 12 weeks
- Ketoconazole – inhibits steps of steroid synthesis
  - Treatment response seen at 8 weeks when patients were given 600 mg daily for 4 weeks

ASRS PAT Survey 2013

Chronic Treatment of CSR

What is your approach to chronic CSR (6 months), Va = 20/20, diffuse leak involving tveas?

- Thermal laser
- Phototherapeutic keratectomy
- Intravitreal injection of triamcinolone
- Intravitreal injection of bevacizumab
- Intravitreal injection of ranibizumab
- Other
- No treatment

Treatment modalities

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- Mifepristone – an antagonist of glucocorticoids and progesterone receptors, inhibits cortisol-induced peripheral vasoconstriction
  - Treatment response seen in 16 patients with chronic CSC treated with 200 mg daily for 12 weeks
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  - Treatment response seen at 8 weeks when patients were given 600 mg daily for 4 weeks

References:

what was statistical method
aantoszyk, 7/17/2013
**Treatment modalities**

- Obstructive sleep apnea treatment – hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system overactivation seen with poor sleep quality may contribute to development of CSC.
- Case report indicates identifying/treating obstructive sleep apnea may allow for resolution of CSC.
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- H. pylori treatment
  - Small case series used metronidazole and amoxicillin 500 mg 3x daily for 2 weeks and omeprazole 1x daily for 6 weeks in CSC patients – treated patients experienced enhanced absorption of SRF compared to control group.

**Verteporfin PDT**

- Probable mechanism:
  - Light-activation of verteporfin (visudyne), a drug used in PDT, selectively occludes choroidal neovascularization and superficial choroidal vessels.
  - Short-term choriocapillaris hypoperfusion.
  - Long-term choroidal vascular remodeling – leading to reduction in choroidal congestion, vascular hyperpermeability, and extravascular leakage.
- Has minimal effects on overlying retina and deeper choroidal layers.

**Summary Of Randomized Trials Since 1990**

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>N</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>Bae SH</td>
<td>32</td>
<td>Low fluence PDT superior to ranibizumab for chronic CSR at 12 months</td>
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<tr>
<td>2013</td>
<td>Roisman L</td>
<td>15</td>
<td>Subthreshold diode micropulse laser superior to sham for chronic CSC at 3 months</td>
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<tr>
<td>2013</td>
<td>Deng Y</td>
<td>53</td>
<td>H. Pylori eradication did not improve acuit or subretinal fluid</td>
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<tr>
<td>2013</td>
<td>Behnia M</td>
<td>37</td>
<td>Macular subthreshold laser therapy improved acuity at 6 months</td>
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<tr>
<td>2013</td>
<td>Semeraro P</td>
<td>22</td>
<td>No significant difference between bevacizumab and low fluence PDT</td>
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<tr>
<td>2013</td>
<td>Rotasauzon M</td>
<td>51</td>
<td>High-dose antioxidants for acute CSC showed no benefit for acuity or thickness</td>
</tr>
<tr>
<td>2011</td>
<td>Wu ZH</td>
<td>34</td>
<td>Half-dose PDT superior to placebo for acuity at 1 year</td>
</tr>
<tr>
<td>2011</td>
<td>Bae SH</td>
<td>16</td>
<td>Reduced-fluence PDT superior to ranibizumab at 3 months</td>
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<tr>
<td>2011</td>
<td>Kall C</td>
<td>30</td>
<td>Selective retina therapy with Nd:YLF laser superior to control at 3 months</td>
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<tr>
<td>2010</td>
<td>Lim JW</td>
<td>24</td>
<td>Bevacizumab similar to observation at 6 months</td>
</tr>
<tr>
<td>2008</td>
<td>Chan WM</td>
<td>63</td>
<td>Half-dose PDT superior to observation for acuity and thickness at 12 months</td>
</tr>
<tr>
<td>2004</td>
<td>Verma L</td>
<td>30</td>
<td>Dye laser superior to argon green laser at 1 month for acuity</td>
</tr>
</tbody>
</table>

**Verteporfin PDT**

- Previous treatments, such as laser photocoagulation, would shorten the duration of symptoms without providing visual benefits or having any impact on the final recurrence rate.
- Also, only targets RPE leak without specifically treating the underlying hyperpermeability.
- May cause RPE damage.
- PDT with verteporfin recently has demonstrated beneficial visual outcomes in most patients.
**Half-fluence PDT**

- “Standard” fluence and dose
  - 83 seconds at an exposure of 600 J/cm² after a 10 min infusion of 6 mg/m² verteporfin dose
- Low “half” fluence/“half” dose
  - 42 seconds after an exposure of 300 J/cm² after infusion of 3 mg/m² of verteporfin dose
- Evidence suggests lower PDT fluence and dosage of verteporfin may be as effective as conventional PDT while minimizing adverse effects.²,⁴,⁶

**Investigating PDT for CSC**

- Previous studies were small in magnitude and may not be reflective of the large-scale impact of verteporfin PDT on chronic CSC patients
- Recent study conducted by Lim et al investigated the outcomes on the largest collection of patient cases with chronic CSC treated with verteporfin PDT.⁷
  - Retrospective case series of 265 eyes
  - Observed visual acuities (VA) over time and presence/absence of subretinal fluid (SRF)

**PDT treatments**

- 94% eyes had 83 seconds treatment duration
- Full-fluence 600 J/cm²
- Half-fluence 300 J/cm²

**Change in visual acuity from baseline VA**

- 4% 4% 1% 1% 1%
- 7% 7% 5% 3% 1%
- 15% 15% 59% 29% 48%
- 20/32 or better
- 20/40 to 20/80
- 20/100 or worse
Verteporfin PDT therapy resulted in improved VA, resolution of SRF, and reduction in FA leakage in the majority of treated eyes.

- Adverse side effects were uncommon: post-treatment acute severe VA decreases occurred rarely (1.5%).
- Prospective studies should be done with an untreated comparison group to validate these findings.
- More large-scale studies are warranted to investigate optimal fluence and dosing.

Case study:
- 55 year old male, previously treated for CSR by referring physician.
- CSR both eyes – was on rifampin orally but liver enzymes increased significantly.
- Pinpoint leakage on FA would be amenable to PDT both eyes.
First visit (VA OS 20/25 -2)

Case study: 1 week follow-up

- PDT OD:
  - 6 mL verteporfin over 10 minutes
  - Fluence: 50 J/cm²
  - Spot size: 3.9 microns
  - Duration: 82 seconds

VA OD 20/250
VA OS 20/30

Case study

<table>
<thead>
<tr>
<th>Month 1</th>
<th>VA OD 20/200</th>
<th>VA OD 20/30</th>
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<tbody>
<tr>
<td>Month 2</td>
<td>VA OD 20/300</td>
<td>VA OD 20/25</td>
</tr>
<tr>
<td>Month 4</td>
<td>VA OD 20/400</td>
<td>VA OD 20/20</td>
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</table>

Eplerenone

- It has recently been proposed that excessive glucocorticoid-dependent choroidal mineralocorticoid receptor (MR) activation in choroidal vessels may be involved in CSCR’s pathogenesis.1,2,3
- Recent case reports have observed eplerenone, an MR antagonist, significantly improving visual and anatomical outcome of patients with CSCR – further investigation with more patients on eplerenone for CSCR is warranted

Methods

- Retrospective analysis on 17 patients with a history of CSCR on eplerenone
- Outcome measures include: LogMar visual acuity, central subfield thickness, cube volume, cube average thickness, horizontal subretinal fluid measurement, and vertical subretinal fluid measurement
- Time to first visit was divided into 4 frames:
  - baseline (0 day to first visit)
  - 0-90 days
  - 91-181 days
  - 181+ days.

Baseline characteristics

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Mean ± Standard Deviation</th>
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<tbody>
<tr>
<td>Age</td>
<td>57 ± 15 years, range 29 – 85 years</td>
</tr>
<tr>
<td>Time on eplerenone</td>
<td>181 ± 81 days, range 38 – 300 days</td>
</tr>
<tr>
<td>Best Corrected Visual Acuity</td>
<td>20/69, range 20/20 – 20/250</td>
</tr>
<tr>
<td>LogMar Visual Acuity</td>
<td>0.42 ± 0.08, range 0 – 1.097</td>
</tr>
<tr>
<td>Central Subfield Thickness (μm)</td>
<td>364.5 ± 40.0, range 211 – 874</td>
</tr>
<tr>
<td>Cube Volume (mm³)</td>
<td>11.2 ± 0.52, range 8.1 – 18.6</td>
</tr>
<tr>
<td>Cube Average Thickness (μm)</td>
<td>312.2 ± 14.5, range 292 – 327</td>
</tr>
<tr>
<td>Subretinal Fluid (μm)</td>
<td></td>
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<tr>
<td>Horizontal diameter</td>
<td>2174.4 ± 1743.8, range 455 – 5520</td>
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<tr>
<td>Vertical height</td>
<td>131.5 ± 248.8, range 43 – 706</td>
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LogMar Visual Acuity

<table>
<thead>
<tr>
<th>Days</th>
<th>Baseline</th>
<th>0-90</th>
<th>91-181</th>
<th>181+</th>
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<tbody>
<tr>
<td>p</td>
<td>0.42 n=17</td>
<td>0.4  n=15</td>
<td>0.31 n=10</td>
<td>0.29 n=8</td>
</tr>
<tr>
<td></td>
<td>p=0.41</td>
<td>p=0.19</td>
<td>p=0.024</td>
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Central Subfield Thickness

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<th>91-181</th>
<th>181+</th>
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<tbody>
<tr>
<td>p</td>
<td>364.5 n=17</td>
<td>331.4 n=15</td>
<td>323.1 n=10</td>
<td>298.7 n=8</td>
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<tr>
<td></td>
<td>p=0.048</td>
<td>p=0.08</td>
<td>p=0.023</td>
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**Cube Volume**

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<tr>
<td>n</td>
<td>17</td>
<td>15</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>p</td>
<td>0.24</td>
<td>0.16</td>
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**Cube Average Thickness**

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<tr>
<td>n</td>
<td>17</td>
<td>15</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>p</td>
<td>0.22</td>
<td>0.13</td>
<td>0.14</td>
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**Subretinal Fluid – horizontal measurement**

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<th>91-181</th>
<th>181+</th>
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<tr>
<td>n</td>
<td>15</td>
<td>13</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>p</td>
<td>0.014</td>
<td>0.002</td>
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**Subretinal Fluid – vertical measurement**

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<th>91-181</th>
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</thead>
<tbody>
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<td>n</td>
<td>15</td>
<td>13</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>p</td>
<td>0.049</td>
<td>0.007</td>
<td>0.16</td>
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</table>
Conclusions

- Eplerenone treatment on CSCR did not significantly improve LogMar visual acuity, but did improve CST, cube volume, and cube average thickness within this cohort

Eplerenone case

- OS: total of 7 Avastin injections OS, little change with injections
- OD: Worsening SRF, stable vision
- Patient begins eplerenone 25 mg qd on 11/07/2012 (about 8 months since initial visit date)

Following Eplerenone

Baseline
- VA (OD): 20/50 +1
- VA (OS): 20/250

Month 1
- VA (OD): 20/40 -1
- VA (OS): 20/200

Month 3
- VA (OD): 20/30 -2
- VA (OS): 20/150

*Patient begins 50 mg

Month 6
- VA (OD): 20/20
- VA (OS): 20/150

Following Eplerenone

Month 6
- VA (OD): 20/20
- VA (OS): 20/150

Month 11
- VA (OD): 20/20
- VA (OS): 20/160 +1

*Patient continues eplerenone 50mg qd

Month 15
- VA (OD): 20/20
- VA (OS): 20/125
Conclusions

- Advancements in diagnostic tests allow for better detection of disease over previous methods.
- For acute phases of the disease, observation alone is sufficient and NSAIDs might hasten anatomic recovery.
- For chronic phases, a variety of treatment options exist:
  - Discontinue inciting agent.
  - Consider adding oral therapy – Eplerenone and Rifampin.
  - Consider PDT – Reduced fluence or Full fluence.
- None of the therapies are approved, so a RCT would be helpful in determining efficacy of these agents.