Update on Retina

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Overview

• Part 1: The Changing Landscape of Central Serous Chorioretinopathy and Related Disorders
  – CSR, Pachychoroid Disease Spectrum
  – AMD - dry and wet
• Part 2: Proliferative Diabetic Retinopathy
Part 1: Fluid and the Macula
Central Serous Chorioretinopathy (CSC)

• First described in 1866
• Incompletely understood, multifactorial etiology
• Young to middle-aged men
• Serous detachment of the neurosensory retina
• Idiopathic etiology
  – May be related to endogenous or exogenous corticosteroid use
Recent Developments

- Description of eyes with pigmentary changes often seen in fellow eyes of CSC patients
- Appeared to occur in the ABSENCE of sub retinal fluid
- Often misdiagnosed as early or atypical age-related macular degeneration (AMD) or inflammatory disease
- Labeled as Pachychoroid Pigment Epitheliopathy (PPE)
Recent Developments

• Wider range of disease manifestations with similar findings
• Increasingly grouped under a common term:
  – PACHYCHOROID DISEASE SPECTRUM
• Evolving group of diseases
• Newer imaging techniques rapidly changing our understanding and approach
Pachychoroid Disease Spectrum

- Central Serous Chorioretinopathy
- Pachychoroid Pigment Epitheliopathy
- Pachychoroid Neovascularopathy
- Polypoidal Choroidal Vasculopathy
Central Serous Chorioretinopathy

• Previously known as Central Serous Retinopathy
• CSCR, CSC, CSR all currently used acronyms
• Idiopathic serous macular detachment
  – May have serous PED (pigment epithelial detachment)
CSC findings

- Bilateral involvement frequent
- Corticosteroid use (or endogenous levels) a risk factor
- FA shows a focal leakage at level of RPE
CSC Late findings

- Chronic or recurrent CSC can persist beyond the sixth and seventh decades
- Atrophic or neovascular sequelae possible
Development of CSC

• Problems with choroidal circulation
• RPE barrier breakdown
  – Leads to fluid from choroid breaking into sub retinal space
Risk Factors for CSC

• Type A behavioral pattern linked to CSC
  – Occupation description often linked
  – Elevated catecholamine levels

• Elevated corticosteroid levels
  – Cushing syndrome (elevated cortisol levels)
  – Multiple mechanisms of effect

• Hypertension, smoking, and alcohol consumption also linked
Features of Typical CSC

- Typically affects males (6:1 predominance)
- Ages: 30 to 50
  - Older age should be concerning for AMD, Polypoidal choroidal vasculopathy (PCV)
- Usually unilateral
  - Chronic cases often bilateral
Presentation of CSC

- Central scotoma, metamorphopsia, blurring of vision
- HYPEROPIC shift in refraction (retina is more anteriorly displaced)
- Loss of foveal reflex
- Can be seen with indirect ophthalmoscopy or with OCT
- More chronic cases - RPE changes common
Differential Diagnosis of CSC

• Optic disc pit
  – Carefully examine the optic nerve on exam and on OCT

• AMD
  – Look for drusen in both eyes
  – Age can be a clue, but not definitive

• Inflammatory and infectious diseases
  – Look for cells in the anterior chamber and vitreous

• Tumors
  – Examine for elevated larger choroidal lesions
Natural History of CSC

• Usually self-limiting

• 90% of cases will show resolution without significant vision loss

• Chronic or recurrent cases can lead to more substantial vision decline

• 50% of patients can have recurrence

• CNV can develop in 6% of cases

• Should not be considered a benign disease
Treatment of CSC

- Natural history is favorable
- Observation usually first line
- Risk factor changes:
  - Cortisone creams, nasal sprays, joint injections of steroids
  - Stopping those treatments can be very effective
  - Smoking cessation
- Symptoms of greater than 3 months duration typically are treated
Active Treatment of CSC

• Foveal damage possible after 4 or more months of symptoms
• No treatment has shown definitive improvement in visual acuity
• Typically used for “chronic” cases where symptoms are notable
Photodynamic Therapy

– Intravenous dye followed by theoretical selective laser application
– May be safer with newer methods of lower laser fluence and verteporfin dye dose
– Generally considered to have favorable outcomes in some CSC patients
– Side effects still possible: RPE atrophy, choriocapillaris ischemia, secondary CNV
Laser Photocoagulation

• Direct laser application to leaking spot noted on diagnostic testing

• Traditional laser mostly fallen out of favor
  – Permanent scotoma, enlarging laser scar, foveal photocoagulation

• More diffuse choroidal abnormalities
  – Laser only focuses on single areas

• Micropulse diode laser may be better suited
  – No reliable randomized trials at present
Oral Treatments: Theory

• Inflammation may have a role in the vessels
  – Traditionally been elimination since steroids are a RISK factor
  – Treatments with steroid still NOT advised

• May be related to mineralocorticoid receptor (MR)
  – Steroids may cause disease by activating this receptor in the choroid
  – Antagonists may be beneficial
Oral Treatments

• Two MRA medications currently used: Eplerenone and Spironolactone
  – Eplerenone more selective - typically less side effects

• General side effects:
  – Gynecomastia, decreased libido, erectile dysfunction

• Laboratory risks:
  – ELEVATED POTASSIUM LEVELS - can lead to heart rhythm changes
  – Changes in kidney function

• Monthly monitoring of potassium levels and kidney function required
Summary of Current Treatments of CSC

• PDT - Effective in some cases, but side effects possible

• Laser - Traditional laser usually avoided; micro pulse laser may be promising

• Intravitreal injections - Generally not as effective, but there may be overlap

• MRA - May become preferred therapy; promising results; side effects have to be monitored

• No FDA approved therapies at present

• Numerous variable studies of each treatment; no definitive large-scale randomized results yet
Pachychoroid Pigment Epitheliopathy

• Form fruste of CSC

• CSC findings without sub retinal fluid
  – RPE pigmentary changes
  – Characteristic thick choroid
    • Comprised of larger outer choroidal vessels: PACHY-choroid
Pachychoroid Neovasculopathy

• Neovascularization seen clinically and on FA
• Known to occur in CSC
• Can be difficult to distinguish from wet AMD
  – Younger age at onset
  – Absence of drusen
  – Thick choroid with pachyvessels
Polypoidal Choroidal Vasculopathy

• Vasculopathy located in the inner choroid
• Best visualized with Indocyanine-Green Angiography (ICG-A)
• Many questions on etiology unknown
PCV - Characteristics

- Strong predilection for patients of East Asian or African ancestry
- Often considered a variant of wet AMD
- Many features overlap with pachychoroid entities:
  - Minimal or absent drusen
  - Thicker choroids
  - Pachyvessels in outer choroid
  - Irregular PEDs
PCV Classic findings

- Single or multiple focal nodular areas during ICG-A
- Orange-red sub retinal nodules with ICG-A hyper fluorescence is pathognomonic
- Branching vascular network on ICG-A sometimes noted
- Hemorrhage more often noted
PCV Treatments

• Neovascularization present
  – Anti-VEGF in combination with PDT may be the best option
  – Studies show better response than with anti-VEGF alone or with PDT alone

• Greater use of ICG-A may lead to more diagnosis and understanding
Summary

- Pachychoroid disease spectrum is evolving
- Currently: PPE, CSC, PNV, PCV
- Aids in understanding of the wide variety of diseases that lead to serosanguinous submacular exudation
- OCT-A, increased use of ICG-A all helping in diagnose conditions
- Ongoing studies will lead to more optimal treatment strategies
Age-Related Macular Degeneration

• Multifactorial etiology: Genetic, environmental, behavioral
• Oxidative stress to RPE, low-grade inflammation, stress-induced cell death
• Update on ongoing studies for dry AMD
• Update on ongoing studies for wet AMD
Dry-AMD

• Lampalizumab
  – Antibody injection to reduce progression of Geographic Atrophy

• Brimonidine
  – Intravitreal implant for neuroprotection
  – Addressing progression of GA
Lampalizumab

• Phase 1 studies: Good safety

• Phase 2 study (MAHALO): 20% reduction in GA progression at 18 months

• Phase 3 studies: CHROMA and SPECTRI
  – Double-masked, global studies comparing lampalizumab to sham injections
  – SPECTRI results - did NOT mean primary endpoint of decreased GA size
  – CHROMA results and additional data pending
Brimonididine

• Cytoprotective and neuroprotective effects well documented

• Exact mechanism of these is unclear

• Topical drop does not penetrate enough to benefit retina and RPE

• Intravitreal sustained implant being investigated

• Promising results in initial Phase 1 and Phase 2 studies

• Current studies ongoing
Wet-AMD

• Current anti-VEGF drugs:
  – Ranibizumab (Lucentis)
  – Aflibercept (Eylea)
  – Bevacizumab (Avastin)

• Limitations:
  – Only 30-40% of eyes gain 15 lines of vision
  – Only ~70% of eyes are fluid-free
  – Continued treatment burden on patients
New Treatments of Wet AMD

• Novel targets:
  – Platelet-derived growth factor (PDGF)
    • Pegleranib-Aptamer (Fovista)
    • Rinucumab
  – Angiopoietin
PDGF-Ab Results

• Rinucumab Phase 2 study did NOT meet target endpoint
• Fovista Phase 3 studies did NOT meet target endpoint
• Ongoing investigations on applications to other retinal diseases
• Anti-PDGF currently does not appear to be an upcoming treatment for wet AMD
Angiopoietin targets

• Angiopoietin appears to play an important role in angiogenesis (CNVM)
• Multiple current Phase 2 studies ongoing
  –AVENUE, STAIRWAY, ONYX
• Results likely coming in next year
Other Investigations

• Numerous other developing studies at earlier stages
• Novel port-delivery system for ranibizumab
  – Implanted refillable port; medication can be periodically filled into device
  – Controlled release of medication over months
  – LADDER trial: Phase 2 ongoing
Summary of AMD

• Dry AMD
  – Smoking cessation
  – Nutrition
  – AREDS 2 Vitamins

• Wet AMD
  – Current anti-VEGF medications

• Numerous developments possible in next 2-3 years
Part 2: Proliferative Diabetic Retinopathy
Diabetes Mellitus: US Prevalence

US Prevalence$^{1,2}$

1. Data on file, Regeneron Pharmaceuticals, Inc.
Diabetes Mellitus

– Nephropathy (kidney disease)
– Neuropathy (peripheral nerves)
– Decreased Healing of Tissues
– Increased risk of infections
– Increased risk of heart attacks
– Retinopathy
• Progressive dysfunction of the retinal vasculature resulting from chronic hyperglycemia¹
• Leading cause of new cases of blindness in U.S. adults ages 20-74²
• Affects 4.2 million U.S. patients²,³

Diabetic Retinopathy

Duration of diabetes is a strong predictor for DR development and progression¹

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>All diabetes</td>
<td>28.5%</td>
</tr>
<tr>
<td>Type 1 Diabetes Mellitus</td>
<td>95%</td>
</tr>
<tr>
<td>≥ 16 years</td>
<td>60%</td>
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Current Screening Guidelines
Timing

• Type I Diabetes
  – Initial Evaluation: 5 years after Diagnosis
  – Follow-up Evaluation: Yearly

• Type II Diabetes
  – Initial Evaluation: At time of Diagnosis
  – Follow-up Evaluation: Yearly
General Guidelines

• Glucose control and blood pressure control are important
  – HbA1C control correlated to retinopathy progression
    • Advise patient to maintain at 7.0 or lower

• Aspirin use IS safe if recommended by doctor
  – No benefit to retina directly (ETDRS)
  – No increased risk of hemorrhages
Causes of Vision Loss

• Diabetic Retinopathy can cause multiple things:
  – Diabetic Macular Edema
  – Macular ISCHEMIA
  – Vitreous hemorrhage
  – Tractional retinal detachments on macula
Severe NPDR

• Severe NPDR is similar to early PDR
• 50% of severe NPDR will develop PDR within 1 year
• 75% of very severe NPDR will develop PDR within 1 year
Proliferative Diabetic Retinopathy (PDR)

- Defined as retinal neovascularization
- From established studies (ETDRS), separate into high-risk PDR and non-high-risk PDR
- Non-high-risk PDR and severe/very severe PDR are very similar
  - High risk of progression
High Risk PDR

- Any neovascularization of the disc (NVD) with vitreous hemorrhage (VH)
- Large area of NVD (>1/3 disc area) with or without VH
- Large area of neovascularization elsewhere (NVE) with VH
Panretinal Photocoagulation

• Laser is applied to a broad area of ischemic retina
• Exact mechanism is not understood
• Decreased factors that induce neovascularization
• Increased oxygen delivery from choroid to retina through thinned retina from laser
• Combination of above factors
• Efficacy of PRP is well established
Treatment of non-high-risk PDR

• Mild and moderate NPDR do not need PRP
• If high-risk PDR is reached, prompt PRP is needed
• For non-high-risk PDR, treatment is individualized
• Follow-up every 3-4 months is important
• Other medical conditions may favor earlier treatment
Presence of DME

• ETDRS showed that DME can be WORSENED by PRP

• Most specialists feel DME should be treated concurrently or initially, prior to PRP

• PRP should not be delayed in high-risk PDR
  – PDR can be the more permanently blinding issue
High risk PDR

- DRS and ETDRS established benefit of performing pan retinal photocoagulation (PRP)
- Usually induces regression of NV
Untreated PDR

• Untreated PDR can progress to severe problems
• Neovascularization can become extensive
• Contraction can pull on the retina
  – Tractional retinal detachment
  – Tears induced - rhegmatogenous retinal detachment
    • “Combination” retinal detachment
Newer insights - Role of Anti-VEGF

• DME Trials showed regression of retinopathy in general with use of anti-VEGF

• Ranibizumab (Lucentis) recent approval for diabetic retinopathy without DME

• Afibbercept (Eylea) trial for this ongoing
Protocol S

- **DRCR.net** Protocol S directly compared ranibizumab to PRP in eyes with PDR

- Anti-VEGF group was not inferior to PRP in progression of PDR

- Anti-VEGF group had significantly better visual field results at 2 years

- Anti-VEGF group had better visual acuity
  - True even in PRP group with DME that received injections
  - PRP may worsen visual acuity independent of DME treatment
Protocol S - Caveats

- Study results only at 2 years - ongoing till 5 years
- Study population had excellent follow-up
- PRP has a proven long-term benefit
- Consideration of insurance, follow-up, control of diabetes, general health very important
- Costs of recurrent visits and repeated injections have to be balanced
Current Opinions

• High-risk PDR should likely continue to have PRP

• Severe NPDR and non-high-risk PDR may need PRP treatment
  – Individualized to patient situation

• Anti-VEGF agents an added good option of treatment
  – Have to be considered by patient situation
Other Situations for PRP

• Neovascularization of the Iris
• Neovascular Glaucoma
  – Can occur just at the angle without significant NVI visible
  – Gonioscopy is necessary
  – Leads to a secondary angle closure
  – May need surgical treatment early
Vitrectomy Surgery

• When extensive tractional effect present, surgery may be necessary
• Macula-involved or macula-threatening tractional disease
• Goal is to relieve the mechanical traction to obtain macular re-attachment
• Challenging surgeries with high risk of complications
Vitrectomy Surgery

• Also indicated with extensive vitreous hemorrhage
  – Precludes proper assessment of the retina
  – Precludes proper laser treatment

• Anti-VEGF injections often used prior to these situations
PDR Summary

• PDR is a devastating complication of diabetic retinopathy
• Can be an irreversibly blinding condition
• Important to counsel patients:
  – Need for follow-ups
  – General health and diabetic control
Retina referrals

• Refer if there is DME
• Refer if there is severe NPDR due to high risk of progression
  – Multiple dot blot hemorrhages in all quadrants
• Refer if there is any indication of PDR: non-high risk or high-risk
References


• AAO PPP Retina/Vitreous Panel. 2016. Diabetic Retinopathy PPP - Updated 2016.


• Rahimy et al. Oral Mineralocorticoid Receptor Antagonists for the Treatment of CSC. Retinal Physician.
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