Retinal Vascular Occlusions

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FEBRUARY 19, 2015
1. Diabetic Retinopathy
2. Hypertensive Retinopathy
3. Retinal Artery Occlusion
4. Retinal Vein Occlusion
5. Sickle Cell Retinopathy
6. Radiation Retinopathy
7. Vasculitis
8. Coat’s Disease
RETINAL ARTERY OCCLUSIONS
Arterial Occlusive Disease
- Retinal ischemia results from disease process affecting the afferent vessels beginning with the common carotid artery to the intraretinal arterioles

Classified into 3 types
- Central Retinal Artery Occlusion (CRAO)
- Branch Retinal Artery Occlusion (BRAO)
- Cilioretinal Artery Occlusion (CLRAO)

All three share similar pathogenesis
- Thrombosis or embolization of the affected vessel
- Leading to blockage, capillary nonperfusion, retinal edema, ischemia, loss of vision
Retinal Artery Occlusions - Pathophysiology

• Review
  ○ Blood supply to the inner layers of the retina derived entirely from central retinal artery
  ○ Unless a cilioretinal artery is present (15-30% of eyes)
  ○ Blockage may affect vessels anywhere from common carotid artery to the intraretinal arterioles
  ○ Signs and symptoms of arterial obstruction depend on vessel involved
  ○ Resulting in: no symptoms to total blindness

• Incidence
  ○ Estimated at 8.5 cases per 100,000
  ○ Largely seen in older adults
  ○ Average age – early 60s
  ○ Men more frequently affected than women
  ○ No prediction of one eye over the other (1-2% bilateral)
Retinal Artery Occlusions - Pathophysiology

- **Risk Factors**
  - Hypertension, carotid artery obstructive disease
  - Cardiac embolic disease, vasculitis, collagen-vascular disease
  - Anemia (severe), trauma

- **Three Main Varieties of Emboli**
  - Cholesterol emboli (Hollenhorse plaques) arising in the carotid arteries
  - Platelet-fibrin emboli associated with large vessel arteriosclerosis
  - Calcified emboli arising from diseased cardiac valves
Retinal Artery Occlusions - Pathophysiology

- Rare Causes of Emboli
  - Cardiac myoma
  - Fat emboli from long bone fractures
  - Septic emboli from infective endocarditis
  - Talc emboli in intravenous drug user

- Other Associations
  - Trauma
  - Coagulation disorders
  - Oral contraceptive use or pregnancy
  - Arrhythmias
  - Inflammatory and infectious etiology i.e. toxoplasmosis, syphilis
  - Connective tissue disorder including giant cell arteritis
  - Mitral valve prolapse
Central Retinal Artery Occlusions (CRAO)

- Represents 57% of all acute RAO
- Presents with sudden, complete, and painless loss of vision
- On exam retina opaque and edematous with cherry red spot

- CRAO often caused by atherosclerosis-related thrombosis
- Emboli present in 20-40% of eyes with CRAO
- With time central retinal artery reopens or recanalizes and retinal edema clears
- Irreversible damage to retina after 90 minutes
Central Retinal Artery Occlusions (CRAO)

- Giant cell arteritis (GCA) accounts for 1-2% of CRAO
  - Consider in cases of CRAO in which emboli not visible
  - ESR and C-reactive protein levels are usually elevated
  - CBC may detect elevated platelet counts
  - Corticosteroid therapy should be started and temporal artery biopsy performed
Central Retinal Artery Occlusions (CRAO)

**Evaluation**
- Etiologic workup on outpatient basis with PCP
- Evaluation of embolic source
  - Carotid doppler imaging – presence or absence of plaque more important than degree of stenosis
  - Echocardiography – cardiogenic cause of emboli less common. TTE results in anticoagulation or cardiac surgery in only 1.5% of patients
  - Hypercoagulability evaluation – Patients <50 yo with suggestive history, i.e. – prior thrombosis, miscarriage, or family history
Central Retinal Artery Occlusions (CRAO) - Treatment

- Potentially Beneficial
  - Reducing IOP by ocular massage
  - Administering IOP-lowering medications
  - Performing anterior chamber paracentesis

- Unlikely to be Beneficial
  - Breathing into paper bag (vasodilatory inhalation)
  - Hyperbaric oxygen therapy
  - Catheterization of the ophthalmic artery with tPA infusion
  - Transvitreal Nd: YAG embolysis
Central Retinal Artery Occlusions (CRAO)

- **Outcome**
  - Spontaneous improvement can occur and has been reported to occur within 3 days of onset
  - Less than 10% of patients report meaningful visual recovery
  - Rarely do patients have complete spontaneous recovery
Branch Retinal Artery Occlusions (BRAO)

- Represents 38% of all acute RAOs
- Presents with monocular vision loss which may be restricted to one part of the visual field
- On exam sectorial pattern of retinal opacification along distribution of the obstructed vessel
- Emboli visible 62% of the time
Branch Retinal Artery Occlusions (BRAO)

- **Management**
  - Directed toward determining systemic etiologic factors
  - Retinal artery emboli linked to increased mortality, therefore systemic and vascular evaluation should be considered
  - No specific ocular therapy has been found to be effective
  - Pressure on globe may dislodge embolus, but efficacy unknown

- **Visual prognosis generally good**
- Acuity usually improves to 20/40 or better in 80% of eyes
- Ultimate vision correlates with degree of foveal involvement
Cilioretinal Artery Occlusions (CLRAO)

- Distinct clinical entity
- Cilioretinal arteries arise from the short posterior ciliary arteries rather than the CRA
- Accounts for 5% of RAO
- Giant cell arteritis should be considered strongly
RETINAL VEIN OCCLUSIONS
Retinal Vein Occlusions (RVO) - Introduction

- 2\textsuperscript{nd} leading cause of blindness from Retinal Vascular Disease
  - Surpassed only by Diabetic Retinopathy
- Classified into 3 types
  - Central Retinal Vein Occlusion (CRVO)
  - Branch Retinal Vein Occlusion (BRVO)
  - Hemi Retinal Vein Occlusion (HRVO)
- All three share similar pathogenesis
  - Thrombus formation within lumen of vessel
  - Leading to venous congestion, retinal hemorrhages, capillary non-proliferation, retinal edema, vision loss
Retinal Vein Occlusions (RVO) - Introduction

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Retinal Vein Occlusions - Introduction

- **Review**
  - Poor visual prognosis
  - Lack of effective vision restoring treatments in past
  - New and creative therapies are now available
  - Treatment previously aimed at site of thrombosis
  - New treatments aimed at preventing damage to retinal tissues allowing time for collateral vessels to develop

- **Incidence**
  - Estimated at 180,000 eyes per year in the U.S.
  - Mean age at onset – 65 years

- **Risk Factors**
  - Hypertension, Diabetes, Hyperlipidemia
  - Atherosclerosis, Open angle glaucoma
Retinal Vein Occlusions - Pathophysiology

(Central) CRVO
region posterior to lamina cribrosa
collateral vessels
lamina cribrosa

(Branch) BRVO

00:33 FA

00:22 FA
Retinal Vein Occlusions - Pathophysiology

Normal VA (20/20)  Loss of VA (variable)

Normal  BRVO

Retinal vein compression and narrowing
→ Turbulent blood flow
→ Thrombus formation
→ Ischemia and hypoxia
→ Increased VEGF production
→ Increased capillary permeability
→ Leakage and edema
→ Vision loss
Contributing Factors:

- Advancing age: 50% of cases 65 years or older, 15% under 45 years
- Systemic Conditions: hypertension, hyperlipidemia, diabetes, smoking, obesity
- Raised IOP
- Inflammatory diseases: sarcoid, lupus, Behçet’s
- Thrombophilic disorders: homocysteinaemia, anticardiolipin antibodies, factor V Leiden, protein C or S deficiencies
Central Retinal Vein Occlusions (CRVO) - Description

- **Occurrence:**
  - Common condition
  - 2 cases per 1,000 > 40 years old
  - 5.5 cases per 1,000 > 65 years old

- **Outcome:**
  - Vision may improve without treatment
  - Better visual outcome associated with better VA at time of presentation

- **Two Forms:**
  - Non-Ischemic CRVO
    - 75% of CRVOs
    - May resolve with good visual outcome
    - <10% recover normal vision; 50% have 20/200 or better
    - May progress to ischemic type
Non-Ischemic CRVO
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- **Two Forms:**
  - **Non-Ischemic CRVO**
    - 75% of CRVOs
    - May resolve with good visual outcome
    - <10% recover normal vision; 50% have 20/200 or better
    - May progress to ischemic type
  - **Ischemic CRVO**
    - Less frequent - more severe form
    - Leads to poor vision outcome; 90% have visual acuity <20/200
    - May progress to retinal neovascularization (60%) and rubeosis/glaucoma (40%)
Ischemic CRVO
Central Retinal Vein Occlusions - Presentation

- Sudden unilateral loss of vision, blurred vision
  - Often noted on awakening
- Non-ischemic:
  - Mild or absent APD
  - Wide spread dot-blot and flame hemorrhages
  - Some disc edema
Central Retinal Vein Occlusions - Presentation

- Ischemic:
  - Severe vision impairment
  - Prominent APD may be present
  - Marked dot-blots and flame hemorrhages, cotton wool spots
  - Disc edema usually more severe
  - May be associated with retinal detachment
Central Retinal Vein Occlusions
Differential Diagnosis

Diabetic Retinopathy
Hypertensive Retinopathy
Ocular Ischemic Syndrome
Radiation Retinopathy
Central Retinal Vein Occlusions - Management

- No proven treatment “cure”
- Treatment options two-fold:
  - Identifying/managing modifiable risk factors
  - Recognizing/treating complications
    - Retina neovascularization – vitreous hemorrhages
    - Iris neovascularization – neovascular glaucoma
    - Macular edema (Macular Hole, cellophane maculopathy)
    - Optic atrophy
- Reduce IOP if elevated
- Begin Aspirin
- Refer 1-3 days
Central Retinal Vein Occlusions - Treatment

**TREATMENT OPTIONS**

- Anti VEGF (Lucentis, Avastin, Eylea) – intravitreal
- Steroids (triamcinolone, Triesence, Ozurdex) – intravitreal
- Sheathotomy
- Radial Optic Neurotomy (RON)
- Laser induced chiororetinal venous anastomoses

**Retinal vein compression and narrowing**

- Turbulent blood flow
- Thrombus formation
- Ischemia and hypoxia
- Increased VEGF production
- Increased capillary permeability
- Leakage and edema
- Vision loss
Retinal Vein Occlusions

- Treatment options
Retinal Vein Occlusions – Clinical Studies

BVOS¹ Laser as SOC (n=139)
CVOS² Observation as SOC (n=155)
SCORE³,⁴ BRVO (n=411) CRVO (n=271)
BRAVO⁵ (n=397) CRUISE⁶ (n=392)
Ozurdex™ approved

Vitrectomy⁸ for RVO and hemorrhage
Vitrectomy⁹
Optic nerve sheath decompression¹⁰
Intravitreal/intravenous thrombolysis¹¹
Artery thrombolysis¹¹
Radial optic neurotomy¹¹
Anti-VEGF
Laser anastomosis¹²
LUCENTIS® approved
Central Retinal Vein Occlusions – Clinical Studies

- Central Vein Occlusion Study (CVOS)
- Standard Care vs. Corticosteroid for Retinal Vein Occlusion (SCORE)
- Ozurdex (Geneva) Study Group
- Study of the Efficacy and Safety of Ranibizumab Injection in Patients with Macular Edema Secondary to CRVO (CRUISE)
Central Retinal Vein Occlusions – Clinical Studies

Central Vein Occlusion Study (CVOS)

- **Recommendations:**
  - Macular grid laser photocoagulation of no visual benefit
  - Observe closely with gonioscopy for development of anterior segment neovascularization
  - Reserve pan-retinal photocoagulation for development of iris neovascularization

Neovascularization in the angle, as seen through an indirect gonioscopy lens.
Central Retinal Vein Occlusions – Clinical Studies

Standard Care vs. Corticosteroid for Retinal Vein Occlusions (SCORE)

- Findings:
  - 1mg and 4mg intravitreal triamcinolone compared to observation
  - 26% of both 1mg and 4mg groups compared to 6.8% (observation group) gained 15 or more letters of better vision
  - Rates of cataract formation and increased IOP (dose dependent) in treatment groups higher than observation group
Central Retinal Vein Occlusions – Clinical Studies

**Ozurdex Study Group**

- Bioerodable implant injected into intravitreal space
- 0.35mg and 0.7mg vs. sham injection
- 41% achieved 15 letter gain at 6 months compared to 23% (with sham)
- Dexamethasone delivered via Ozurdex implant available to the back of eye for up to 6 months
- 20% of patients required no reimplantaion
Central Retinal Vein Occlusions – Clinical Studies

Study of the Efficacy and Safety of Ranibizumab injection in Patients with Macular Edema Secondary to CRVO (CRUISE)

- 28-Day Screening Period
- 1:1:1 Randomization
- Sham (n=130)
- Ranibizumab 0.3 mg (n=132)
- Ranibizumab 0.5 mg (n=130)

Monthly Injections (Day 0, Months 1, 2, 3, 4, 5)

6-Month Treatment Period
6-Month Observation Period

Ranibizumab 0.5 mg
Ranibizumab 0.3 mg
Ranibizumab 0.5 mg

Month 6 Primary Endpoint
Central Retinal Vein Occlusions – Clinical Studies

Study of the Efficacy and Safety of Ranibizumab injection in Patients with Macular Edema Secondary to CRVO (CRUISE)

- Rapid resolution of macular edema and gains in visual acuity
  - Decreased macular edema, increased 7 to 8 letters by one week
- At 6 months visual improvement
  - 12.7 letters (0.3mg); 14.9 letters (0.5mg); 0.8 letter (sham)
- Reduce central foveal thickness (CFT)
- Increased percentage of patients with final vision greater than 20/40

Baseline Visual Acuity

After 15 letter Visual Acuity Gain

HVZDS
NCVKD
CZSHN
ONOVR
KDNRO
ZKCSV

HVZDS
NCVKD
CZSHN
ONOVR
KDNRO
ZKCSV
Central Retinal Vein Occlusions – Clinical Studies

Study of the Efficacy and Safety of Ranibizumab injection in Patients with Macular Edema Secondary to CRVO (CRUISE)

Proportion of Patients who Gained ≥15 Letters from Baseline BCVA
Central Retinal Vein Occlusions

- **Case #1:** Observation

Central Retinal Vein Occlusions

- Case #2: Intravitreal Steroids
Central Retinal Vein Occlusions

- Case #3: Intravitreal Lucentis
Central Retinal Vein Occlusions

- Case #4: Intravitreal Lucentis
Branch Retinal Vein Occlusions (BRVO) - Description

- BRVOs 3 times more common than CRVOs
- Various sub classifications depending on branch affected (major, minor, peripheral)
- Each form carries its own prognosis based on proximity to macular drainage area
Branch Retinal Vein Occlusions - Presentation

- Depends on amount of compromise to macular drainage
- Unilateral, painless blurred vision, metamorphopsia, visual field defect (central, altitudinal)
- Peripheral occlusions may be asymptomatic
- Visual acuity depends on degree of macular involvement
- Vascular dilation, tortuosity, and retinal hemorrhages in area of affected vessels
Branch Retinal Vein Occlusions - Complications

- Complications similar to those with CRVO
  - Macular edema, retinal neovascularization, vitreous hemorrhage
- New vessels tend to occur only when at least one quadrant of the retina is affected
  - Appear about 6 months after original occurrence
- Rate of complication for HRVO is greater than BRVO but less than CRVO
- Over half develop macular edema and 20% may develop retinal neovascularization
- Outcome is reasonably good depending on number of collateral veins that develop
- 50% of patients return to 20/40 or better
Management/Treatment:
- Begin Aspirin
- Refer 1-3 days
- Management depends on area and degree of occlusion
- Observation
- Laser treatment potentially necessary for macular edema and required for peripheral neovascularization
- Steroids (triamcinolone, Triesence, Ozurdex implant) – intravitreal
- Anti-VEGF drugs (Lucentis, Avastin, Eylea) – intravitreal
- Pars plana vitrectomy
- Arteriovenous Sheathotomy
Branch Retinal Vein Occlusions – Clinical Studies

- Branch Vein Occlusion Study (BVOS)
- Standard Care vs. Corticosteroid for Retinal Vein Occlusion (SCORE)
- Ozurdex (Geneva) Study Group
- Study of the Safety and Efficacy of Ranibizumab Injection Compared with Sham in Patients with Macular Edema Secondary to BRVO (BRAVO)
Branch Retinal Vein Occlusions – Clinical Studies

Branch Vein Occlusion Study (BVOS)

● Outcome:
  ○ 1/3 of untreated patients had spontaneously improved vision
  ○ Photocoagulation double the odds of improved vision compared to observation
  ○ Although vision generally improves among patients, improvement beyond 20/40 is uncommon

● Recommendations:
  ○ Macular grid laser photocoagulation for BRVO-related macular edema persisting 3 or more months with vision 20/40 or worse
  ○ Scatter laser photocoagulation recommended upon discovery of posterior segment neovascularization
Standard Care vs. Corticosteroid for Retinal Vein Occlusion (SCORE)

- **Outcome:**
  - 1mg and 4mg triamcinolone injections vs. laser photocoagulation
  - 25.6% (1mg group); 27.2% (4mg group); and 28.9% (laser group) gained 15 or more letters of vision by end of study
  - 25% (1mg group); 35% (4mg group); and 13% (laser group) developed cataracts
  - Significantly higher risk of increased IOP in 1mg and 4mg groups (4mg>1mg)

- **Findings:**
  - Intravitreal steroids beneficial
  - Laser slightly more effective and had superior safety profile
Branch Retinal Vein Occlusions – Clinical Studies

Ozurdex Study Group

- Findings:
  - 41% of patients achieved a 15 letter gain at 6 months compared with 23% of patients who received sham injection
  - Best corrected visual acuity occurred within 2-3 months which was significantly faster than sham group
  - Duration of effectiveness persisted 1-3 months
  - Increased risk of cataracts and increased IOP
Branch Retinal Vein Occlusions – Clinical Studies

Study of the Safety and Efficacy of Ranibizumab Injection Compared with Sham in Patients with Macular Edema Secondary to BRVO (BRAVO)

- Monthly PRN ranibizumab for all patients
- Rescue Laser (if eligible beginning at month 9)

Macular Edema Secondary to BVO

28-Day Screening Period

1:1:1 Randomization

- Sham (n=132)
- Ranibizumab 0.3 mg (n=134)
- Ranibizumab 0.5 mg (n=131)

Monthly Injections (Day 0, Months 1, 2, 3, 4, 5)
- Rescue Laser (if eligible beginning at month 3)

Month 6
Primary Endpoint

6-Month Treatment Period

6-Month Observation Period
Branch Retinal Vein Occlusions – Clinical Studies

Study of the Safety and Efficacy of Ranibizumab Injection Compared with Sham in Patients with Macular Edema Secondary to BRVO (BRAVO)
- Rapid resolution of macular edema and gains in visual acuity
- At 6 months visual improvement
  - 16.6 letters (0.3mg); 18.3 letters (0.5mg); 7.3 letters (sham)
- Reduced central foveal thickness (CFT)
- Increased percentage of patients with final vision greater than 20/40
Branch Retinal Vein Occlusions – Clinical Studies

Study of the Safety and Efficacy of Ranibizumab Injection Compared with Sham in Patients with Macular Edema Secondary to BRVO (BRAVO)

Mean Change from Baseline BCVA over Time to Month 12

- Sham/0.5 mg (n=132)
- 0.3 mg Ranibizumab (n=134)
- 0.5 mg Ranibizumab (n=131)

Mean Change from Baseline BCVA (ETDRS Letters)

Day 0–Month 5
Monthly Treatment

Month

Months 6–11
PRN Treatment

- +18.3*
- +16.4**
- +12.1

+18.3**
Branch Retinal Vein Occlusions

- Case#1: Laser for Macular Edema
Branch Retinal Vein Occlusions

- Case#2: Intravitreal Steroids
Branch Retinal Vein Occlusions

- Case #3: Intravitreal Lucentis
Case#4: Intravitreal Avastin

-37d VA=0.3
-9d VA=0.8
26d VA=0.1
54d VA=0.3

96d VA=0.1
A
152d VA=0.3
A
195d VA=0
250d VA=0
Retinal Vein Occlusions

- **Medical Evaluation**
  - Individuals **55** and older – RVO often related to systemic hypertension and are not associated with a systemic hypercoagulable, inflammatory or infectious disorder
  - Typical presentation should prompt referral to PCP for evaluation of BP, DM and general systemic health
  - Bilaterality, younger age or other atypical features should stimulate further investigation for systemic disease
  - Basic workup: BP, blood glucose, lipid profile, CBC, and ESR
  - Additional workup: thyroid function, CRP, serum ACE, CXR, autoantibodies, antiphospholipid antibodies, Lupus, anticoagulant, homocysteine levels, folate and vitamin B-12 levels, factor 5 Leiden, and antithrombin 3 abnormality
Retinal Vein Occlusions

- **Treatment Considerations**
  - When do you start and how often do you follow?
  - How often does treatment need to be repeated?
  - Is “as needed” treatment sufficient?
  - When can treatment be discontinued?
  - Consideration of glaucoma history or lens status - Does it play a role?
  - Financial Concerns?
  - What factor does work considerations and evaluation of function play in initiating and continuing treatment?
  - Benefit of combination therapy for RVO?
Retinal Vein Occlusions - Conclusions

- Both BRVO and CRVO are frequent causes of vision loss
- Various treatment modalities not previously available now offer hope to patients
- Current treatments are under ongoing evaluation to determine their appropriate use and ultimate benefit
- Standard of care of RVOs is **EVOLVING**