INTRODUCTION TO RETINAL VASCULAR DISEASE – VENOUS/VENULAR

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CENTRAL RETINAL VEIN OBSTRUCTION

CENTRAL RETINAL VEIN OBSTRUCTION / OCCLUSION (CRVO)

- Obstruction of the central retinal vein (at the lamina cribrosa)
- Clinical observations
  - Retinal hemorrhages in all four quadrants.
  - Dilated, tortuous veins in all four quadrants.

CRVO – ADDITIONAL FEATURES / COMPLICATIONS

- Optic disc edema
- Macular edema
- Macular subretinal fluid
- Cotton-wool spots
- Capillary nonperfusion

CRVO – ADDITIONAL FEATURES

- Neovascularization of the iris, retina, or optic disc
- Neovascular glaucoma
- Optic disc venous-venous collateral vessels (opticociliary [collateral] shunt vessels)
- Exudative retinal detachment in severe cases.

CRVO – ADDITIONAL FEATURES

- Optic disc edema*
- Capillary nonperfusion**

*indistinct disc margins

** dim (not blocked [splinters]) areas
GENERAL FEATURES (OF CRVO)
- Common (second only to DR among retinal vascular diseases)
- Rare < 50 years
- Easily recognized!
- Treatment is for the complications (locally) and for the underlying cause (systemically)

VEIN OBSTRUCTIONS - CLASSIFICATION
- Central (CRVO)
  - Ischemic (* ~ 66% develop INV and NV glaucoma)
  - Non-ischemic
- Geographically
  - Central
  - Branch
  - Hemi
  - Macular

CRVO – SYSTEMIC ASSOCIATIONS
- Risk Factors
  - Diabetes mellitus
  - Systemic arterial hypertension
  - Atherosclerotic cardiovascular
- Protective associations
  - Alcohol consumption
  - Education
  - Physical activity
  - Estrogen supplementation (†)

OPHTHALMIC RISKS / ASSOCIATIONS (CRVO)
- Glaucoma – Why?
- Thrombus formation within the LC (theoretical)
  - Atherosclerosis
  - Endothelial cell proliferation / damage
  - Secondary to compression and ensuing changes

OPHTHALMIC RISKS / ASSOCIATIONS (CRVO)
- Based on FA, territories [10 Disc Areas, DA] of retinal capillary non-perfusion – controversial but is the basis for follow-up
- CRVOSG (study group)
  - 2% of NON – ischemic have NV
  - BUT, 34% of NI convert within 3 years
  - And, 15% within the first 4 months

ISCHEMIC VS. NON-ISCHEMIC CRVO
- Thrombus formation within the LC (con’t)
  - Implicated hemodynamic abnormalities
    - Low flow rate
    - Elevated ESR, hematocrit, homocysteine, fibrinogen, viscosity
    - Presence of lupus anticoagulant
    - Deficiency of activated protein C
**ISCHEMIC VS. NON-ISCHEMIC CRVO**

- Clinical picture may resolve in 6-12 mo. But may persist for 7 years.
- But cystoid macular edema (CME) may persist.

**CME IN CRVO**

- Current standard - observation (SCORE)¹
- When persistent
  - Vision loss +
    - Pigmentary changes
    - Epiretinal membrane formation
    - Subretinal fibrosis
- Alternative may be intravitreal anti-VEGF agents (more later)


**CME IN CRVO - SCORE¹**

- Compared to standard (observation), patients with CME from CRVO did better with either 1 or 4 mg IVTA but fewer SEs with 1 mg.

**ISCHEMIC CRVO**

- AKA
  - Severe
  - Complete
  - Total vein obstruction
  - Hemorrhagic retinopathy
- Accounts for 20-25% of all CRVOs

**ISCHEMIC CRVO**

- Acute markedly decreased VA is the rule (rarely better than 20/200* [key clinical finding for NV, CRVOSG])
- RAPD
- Pain is present with NVG

**ISCHEMIC CRVO**

- Distinct clinical appearance
  - Tortuous retinal veins
  - Cotton wool spots
- *Extensive retinal hemorrhages (4 Q) which may obscure fundus details
**ISCHEMIC CRVO**
- Macular edema**
- Vitreous hemorrhage
- *Optic disc edema

**HEMICENTRAL RVO**
- As the name implies, superior or inferior branch of the retinal circulatory system is involved and occurs as an anatomical variant of CRVO but behaves similarly to CRVO in terms of visual outcome, risk of NV, etc.

**RECOMMENDED MEDICAL AND OPHTHALMIC WORK-UP FOR CENTRAL RETINAL VEIN OBSTRUCTION**
- Complete history and physical examination
- Complete ophthalmic examination
- Fluorescein angiography
- Gonioscopy to look for iris and/or angle neovascularization

**RECOMMENDED MEDICAL AND OPHTHALMIC WORK-UP FOR CENTRAL RETINAL VEIN OBSTRUCTION**
- Blood pressure
- Complete blood count
- Prothrombin time
- Partial thromboplastin time
- Antinuclear antibodies
- Serum protein electrophoresis
- Erythrocyte sedimentation rate

**most cause of vision loss in CRVO!**

NVG is a significant risk!
- Onset 60-90 days
DIFFERENTIAL DIAGNOSES
- Retinopathy secondary to long-standing carotid occlusive disease
  - May be confusing and overlapping to some extent
    - (Sometimes AKA venous stasis retinopathy)
  - Carotid artery disease may be characterized by difficulty with dark adaptation
  - Carotid artery disease rarely has associated disc edema

Differential diagnoses
- Hyperviscosity syndromes (sickle-cell, polycythemia vera, leukemia, multiple myeloma, for example)
  - More likely to be bilateral than true CRVO
- Severe anemia and thrombocytopenia may be masqueraders
  - Differentiate with blood testing (CBC w/ platelet count)
- Rule out severe hypertensive retinopathy (compare clinical presentation earlier)

SYSTEMIC ASSOCIATIONS (CENTRAL & HEMI RVO)
- Hypertension
- Diabetes mellitus
- Cardiovascular disease
- Blood dyscrasias
  - Polycythemia vera
  - Lymphoma
  - Leukemia
- Para- and dysproteinemias
  - Multiple myeloma
  - Cryoglobulinemia
- Vasculitis secondary to
  - Syphilis
  - Sarcoidosis
- Autoimmune
  - Systemic lupus erythematosus

MANAGEMENT OF SYSTEMIC ASSOCIATIONS / OPHTHALMIC CONSEQUENCES (OF C/HRVO)
- Blood thinners
- Anti-inflammatory therapy
- Optic nerve sheath decompression
- Plasmaphoresis
- None has proven to be effective

NEOVASCULAR GLAUCOMA
- CRVOSG
  - Prompt panretinal photocoagulation (PRP) for iris NV
- Prophylaxis is NOT universally indicated
NEOVASCULAR GLAUCOMA

- CRVOSG
- Frequent follow-up to identify iris NV
- Recall risk factors (20/200 or worse VA and ischemic territory > 10 DA on FA)

Inferior PRP (note disc neo)

CME (CYSTOID MACULAR EDEMA) IN CRVO

- Treatment alternatives
- CRVOSG
  - Panretinal photocoagulation – X
  - Reduced angiographic NV but no significant VA ↑

CME (CYSTOID MACULAR EDEMA) IN CRVO

- SCORE 5
  - Observation vs.
    - 1 vs 4 mg intravitreal triamcinolone
    - VA improved by 15 or more letters from baseline at 12 mo in both treatment groups but IOP and cataract was greater in the 4 mg group
  - Recommendation: 1 mg IVTA

Ozurdex® (dexamethasone intravitreal implant, Allergan) approved 06/18/2009 [see later]

CONFUSIONS OF CRVO TREATMENTS

- PRP
  - Loss of VF and DA

Ozurdex video:
http://eyetube.net/videos/default.asp?pohila

IVTA
- Increased IOP
- Conjunctival hemorrhage
- Pain
- Hyperemia

PVD
- IVTA videos
http://www.youtube.com/watch?v=ApuxGry2fWv

HA
- http://www.youtube.com/watch?v=AtzX69zquox


CYSTOID MACULAR EDEMA

- CME in BRVO; note macular involvement
  - VA – 20/200

- CME in CRVO; note macular involvement
  - VA – 20/200

OCT OF CME

- Note
  - Inverted foveal pit
  - Cystic spaces
  - Disrupted macula
  - Intact RPE
FOLLOW-UP FOR PATIENTS WHO HAVE CENTRAL RETINAL VEIN OBSTRUCTION

PRESENTING VISUAL ACUITY OF 20/40 (6/12) OR BETTER
- Examinations every 1–2 months for 6 months after diagnosis
- Annual examinations as the patient’s condition stabilizes

FOLLOW-UP FOR PATIENTS WHO HAVE CENTRAL RETINAL VEIN OBSTRUCTION

PRESENTING VISUAL ACUITY BETWEEN 20/50 - 20/200
- Examinations monthly to biomonthly (at the physician’s discretion, based on which end of the spectrum the visual acuity lies) for the first 6 months after diagnosis
- Examinations every 6 months to yearly afterward

FOLLOW-UP FOR PATIENTS WHO HAVE CENTRAL RETINAL VEIN OBSTRUCTION

PRESENTING VISUAL ACUITY OF 20/200
- Examinations every month for the initial 6 months
- Then every 2 months until 8 months after presentation
- Then every 4 months until 2 years after presentation

RECOMMENDED MEDICAL AND OPHTHALMIC WORK-UP FOR BRANCH RETINAL VEIN OBSTRUCTION

- Complete history and physical examination
- Complete ophthalmic examination
- Fluorescein angiography
- Blood pressure

RESOURCE / SUMMARY (BRANCH RVO)

- Abnormal A/V crossing within the retinal circulation with compression of the vein by the artery.
- Good prognosis
  - > 50% have final VA of 20/40

**Epidemiology / Classification**
- More common than CRVO (<2% of gen pop)
- Patient is generally between 60 and 70
- Usually involves ST branch (66%); IT = ~25%
- Cumulative probability of second eye involvement w/in 4 years = ~7%

**Pathogenesis**
- Compression of the vein at the overlying arteriolar crossing secondary to arteriolar disease
- Degenerative changes of the vessel wall (thrombus formation)
- Abnormal hematologic factors may contribute

**Pathogenesis**

Note blocked fluorescence and mild hyperfluorescence in this small BRVO

**Hematologic Factors**
- Coagulation and anticoagulation disorders in the etiology of BRVO
  - Resistance to activated protein C (especially factor V)
  - Leiden mutation
  - Protein C or protein S deficiency
  - Deficiency of antithrombin III
  - Genetic mutation in the prothrombin (factor II) gene
  - Anti-phospholipid antibodies
  - Hyperhomocysteinemia
- Look familiar?

**Clinical Features**
- Dilated, tortuous veins
- Cotton-wool spots
- Macular edema

**Additional Risks / Associations of BRVO**
- Toxoplasmosis
- Eales' disease
- Behçet's syndrome
- Ocular sarcoid
- Coats' disease
- Retinal capillary hemangiomas
- Retinal arteriolar macroaneurysms (RAM)
- Optic disc drusen
- Glaucoma
SYMPTOMS AND SIGNS OF RVO (IN GENERAL)
- Painless vision loss or VF deficit
- VA 20/20- HM
- Hemorrhages point to the obstruction and are flame shaped
- Cotton-wool spots
- Intraretinal edema (which segment?)
- Macular edema
- Retinal NV (~ 20%) and may occur years later

CLINICAL COURSES
- Macular edema
- Neovascular glaucoma (20%); usually < 6 mo.; but may be years later
- Vitreous hemorrhage (may obscure retinal capillary non-perfusion)
  - Vitrectomy
  - Traction RD

CLINICAL COURSES
- Collateral (shunt) vessel development (may cross the raphe)
- Inciting retinal arteriolar sheathing and narrowing/ sclerosis
- Epiretinal membrane formation and pigmentary remodeling secondary to chronic CME

CLINICAL COURSES
- Macular edema
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CLINICAL MANAGEMENT OF RVO
- VA
- Dilated Fundus examination
- Rule out macular edema (?OCT)
  - Fluorescein angiography
- Complete history and systemic workup
- Evaluate BP / BP control if treated
- Consider blood work as indicated
DIFFERENTIAL DIAGNOSES

- Hypertensive retinopathy
- Diabetic retinopathy
- Ocular ischemic syndrome
- Juxtafoveal retinal telangiectasia
  (note remodelling of RPE and leakage on FA)

DIFFERENTIAL DIAGNOSES

- Combined branch retinal artery and branch retinal vein occlusion
- Radiation retinopathy

SYSTEMIC ASSOCIATIONS

- EDCCS (Eye disease case control study) Risks
  - 50% (of BRVO) associated with systemic hypertension
  - History of CVD
  - Increased body mass index (at age 20°)
  - Glaucoma (WHY?)
  - Elevated serum α2-globulin

- Protective associations
  - Alcohol consumption
  - Higher ratio of HDL

OPHTHALMIC TREATMENT OPTIONS (CME)

- Grid photoacoagulation
  [BVOSG guideline, 1997]

- SCORE 6 (2009)
  - Compared standard
  - 1 and 4 mg IVTA
  - No differences in VA outcomes
  - More frequent SE in 4 mg IVTA

NEW CME TREATMENT OPTIONS

- Anti-VEGF agents (intravitreal administration – recall videos)
- Some promise @ 6 months that rival IVTA results for BOTH CRVO and BRVO CME

- Summary of CME from RVO (12/2009)

- BRAVO and CRUISE (Lucentis® intravitreal)
  (3-line improvement @ 6 mo)

CME RESOLUTION FOLLOWING BRVO

CME RESOLUTION (S/P 4 MG IVTA)

CASE EXAMPLES

45 F
- VA = 20/20
- Normal history
- Baseline photo 2000
- Predisposing conditions to retinal vein obstruction?

52 W F
- Sudden onset of reduced VA (X 7½ yrs)
- 20/80 w/central disturbance
- What are you going to do?

*MOST PREVALENT COAGULATION AND ANTI-COAGULATION DISORDERS IN BRVO*

- Resistance to activated protein C (especially factor V Leiden mutation)
- Protein C or protein S deficiency
- Deficiency of antithrombin III
- Genetic mutation in the prothrombin (factor II) gene
- Anti-phospholipid antibodies
- Hyperhomocysteinemia


9/4/2008
Involvement confined to the inner retina
9/9/2008
Cystoid macular edema; Started on Xibrom (bromfenac) qid

52 W F
9/22/2008
VA 20/200; distinct macular involvement; Now what?

52 W F
1/14/2009
Continued on Xibrom qid Some resolution

52 W F
1/19/2009
Continued on Xibrom qid

52 W F
2/17/2009
Continued on Xibrom qid
Uninvolved OS

Recommend anti-VEGF intravitreal injection

VF 2/24/2009
And an Avastin injection
VA = 20/25!!!
Restoration of normal anatomy
**TREATMENTS FOR ME FOLLOWING RVO**

- **SCORE 5**
  - CRVO – standard care = observation
  - Neither 1 mg nor 4 mg IVTA offered better outcome

  SCORE SRG Arch Ophthalmol 2009; 127; 1101.

- **SCORE 6**
  - BRVO – standard care = grid photocoagulation
  - Both 1 mg and 4 mg IVTA showed 15-letter gains in ~25% of eyes @ 12 mo.
  - Fewer IOP elevations and cataract in the lower dose

**BUT WAIT! THERE'S STILL MORE!!!**

- **CRUISE**
  - CRVO intervention for CME trial 0.3 or 0.5 mg intravitreal ranimizubab (Lucentis)
  - 46.2 and 47.7% of eyes gained ≥15 letters @ 6 mo. (1.1 in the sham group)

  Retina Congress September 2009
  NYC

- **BRAVO**
  - BRVO intervention for CME (same dosing as CRUISE)
  - 55.2 and 61.1% of eyes demonstrated ≥15 letters @ 6 mo. (1.9 in the sham group)

**HCRVO 44 BM**

History

VA = 20/XXX

Note:
1. Bleeding
2. Fluid = CME
3. Striations
4. H & E
5. AV config

**HCRVO 44 BM**

Management
What are your observations?

Arterial attenuation, sclerosis, disc edema, pale retina, resolving macular exudates

FA @ 49 sec fails to reveal retinal perfusion

@ 1 month
- Disc edema
- Dilated tortuous veins
- Thin arteries
- Intraretinal hemorrhages
- Retinal pallor