TACKLING NEOVASCULAR GLAUCOMA

ASCRS Annual Meeting

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Disclosure

• I have no financial interests or relationships to disclose
Neovascular Glaucoma: Definition

• Secondary glaucoma
• Neovascularization of the iris and/or anterior chamber angle with increased IOP
• Most frequently related to severe, profound retinal ischemia
  • Ischemic CRVO
  • PDR
  • Ocular ischemic syndrome

Background

• Rubeosis iridis noted in 1906 by Coats in eyes with CRVO
• NVG noted previously as hemorrhagic glaucoma, congestive glaucoma, thrombotic glaucoma, rubeotic glaucoma
• Termed neovascular glaucoma in 1963 by Weiss and colleagues

Neovascular Glaucoma

• Neovascular glaucoma (NVG), classified as a secondary glaucoma, was first described in 1871.1

• Depending on the amount of angle involvement, NVG can cause glaucoma through either secondary open-angle or secondary closed-angle mechanisms.1

• Retinal hypoxia stabilizes and dimerizes hypoxia inducible factor-1α, which binds to the promoter region of the VEGF gene and up-regulates synthesis.

• VEGF interacts with blood vessels resulting in new vessels at the pupillary border, iris surface and at the anterior segment angle accompanied by fibrous membranes.1


NVG Pathophysiology

• Can present as a secondary open-angle or closed-angle
• Normally VEGF and IL-6 levels are in equilibrium with pigment epithelium-derived growth factor (PEDF), an antiangiogenic factor
• When the equilibrium between VEGF and PEDF is shifted in favor of VEGF and IL-6, this leads to neovascularization of the anterior segment

Pathophysiology

• Neovascularization has vessel walls with increased permeability due to the absence of tight junctions
• Vessels can cross the scleral spur and obstruct the trabecular meshwork
• Fibrovascular membrane formation can occur causing PAS formation and progressive angle closure

Neovascular Glaucoma

• These membrane may be invisible on gonioscopy, but obstruct the trabecular meshwork causing secondary open-angle glaucoma.
• In the later stages, it cause peripheral anterior synechiae, progressively closing the anterior chamber angle and causing an intractable elevation of intraocular pressure

Etiologies of NVG

<table>
<thead>
<tr>
<th>Retinal ischemia</th>
<th>Retinal Detachment</th>
<th>Ocular Inflammation</th>
<th>Intracocular Tumors</th>
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<tbody>
<tr>
<td>Central retinal vein occlusion</td>
<td>Chronic traction retinal detachment</td>
<td>Chronic uveitis</td>
<td>Choroidal melanoma</td>
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<td>Diabetic retinopathy</td>
<td>Proliferative vitreoretinopathy</td>
<td>Retinal vasculitis</td>
<td>Iris melanoma</td>
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<td>Exudative retinal detachment (central artery occlusion)</td>
<td>コントラクティブ retinopathy</td>
<td>Trauma</td>
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<td>Sickle cell retinopathy</td>
<td>Retinocochisis</td>
<td>Anterior segment ischemia</td>
<td>Metastatic disease</td>
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<td>Central retinal artery occlusion</td>
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<td>Radiation treatment</td>
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<td>Retinopathy of prematurity</td>
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<td>Eales disease</td>
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<td>Familial exudative vitreoretinopathy</td>
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<td>Persistent hyperplastic primary vitreous</td>
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Taken from: Glaucoma: Science and Practice by John Morrison and Irvin Pollack
Differential Diagnosis of NVG

### Symptoms

- Asymptomatic
- Eye pain
- Eye redness
- Photophobia
- Decreased vision

### Signs

**Stage 1:**
- Nonradial, misdirected blood vessels along the pupillary margin and/or TM
- Usually no signs of glaucoma

**Stage 2:**
- Stage 1 plus increased IOP

**Stage 3:**
- Partial or complete angle-closure caused by fibrovascular membrane
- NVI is common

### Other Signs

- Anterior chamber cell and flare
- Conjunctival injection
- Corneal edema
- Hyphema
- Ectropion uvea
- Optic nerve cupping
- Visual field loss

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**Work-Up**

- **History**
  - Diabetes, HTN, etc.
- **Complete eye exam**
  - Gonioscopy
  - UBM
- **Fluorescein angiography**
  - Identify underlying retinal abnormality
- **Carotid Doppler**
  - If no retinal etiology identified
- **B scan**
  - When retina cannot be visualized

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**History and NVG**

- **Diabetes**
  - NVG correlates with glucose control
  - Diabetes Control Complications Trial (DCCT)
    - 24% incidence of NVG in standard treatment group
    - 8% incidence in intensive group
- **CRVO**
  - Vision loss is painless over 60 to 90 days
- **Ischemic**
  - Carotid artery occlusion on same side
  - Elevated IOP

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**Disclosure**

- I have no financial interests or relationships to disclose
- **Acknowledgements**
  - Robert Weinreb, MD
  - Kaweh Mansouri, MD
Neovascular Glaucoma

- NVG is seen in 2.1% in all diabetics. ¹
- CRVO causes 36%, PDR 32% and OIS 13%.
- Course of neo-vascularisation is unpredictable; it can progress rapidly in weeks to NVG, or remain stationary for years or may regress spontaneously.

¹. Frank RN. Diabetic retinopathy. In Ryan ST, Smith RE, eds

Neovascular Glaucoma

- Early diagnosis of NVG, recognition of the causative retinal disease, and aggressive treatment is essential to prevent loss of vision and retain the eye.
- Gonioscopy should be done in all high risk patients periodically.
- NVA may appear before NVI.
- Abnormal blood vessels cross the scleral spur and trabecular meshwork. ¹

¹. Chandler PA, Grant W. Lectures on Glaucoma, Philadelphia: lea and Febiger, 1965

Open-angle glaucomas

- Filtering surgery
- Trabeculectomy
- Ab externo Schlemm’s Canal
- Suprachoroidal Trabecular Meshwork microstents (iStent, Hydrus)
- Gold Shunt Suprachoroidal microstents (Cypass)
- Eyepass Subconjunctival microstent (AqueSys)
- Tube shunt surgery (Ahmed, Baerveldt, Molteno)

Alternative incisional glaucoma surgery

- Trabeculotomy/goniotomy (Trabectome)
- Laser trabeculoplasty
- Deep sclerectomy/viscocanaloplasty
- Canolaplasty

Gonioscopy should be done in all high risk patients periodically.

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¹. Chandler PA, Grant W. Lectures on Glaucoma, Philadelphia: lea and Febiger, 1965
Neovascular glaucoma

- PRP/Anti-VEGF
- Surgery
- CPC/Cryo

- GDD (AGV, Baerveldt)

Trabeculectomy

- Partial thickness scleral flap over a fistula to facilitate flow of aqueous into subconjunctival space
- Following trabeculectomy, aqueous fluid drains subconjunctivally and is absorbed by conjunctival and episcleral veins. The presence of conjunctival microcysts indicates a functioning bleb

Microcysts after trabeculectomy (ASOCT)

Trabeculectomy-NVG

- Shown to be ineffective with frequent complications, bleeding and scarring of the fistula. ¹
- Failure rate of 80% in regular trabeculectomy, with use of antifibrotic success is 28% for 5 years. ¹
- Using injections of 5-FU subconjunctivally in the postoperative period, the surgical success has been reported to be 68% over three years. ¹

Prognostic Factors for Failure

- Younger age, previous vitrectomy, having a fellow affected, disease caused by diabetic retinopathy, and persistent proliferative membrane and/or retinal detachment after vitrectomy. ¹
- Recent studies with intracameral ranibizumab injection (0.5 mg) with subsequent MMC augmented trabeculectomy proved to be an effective combined technique in controlling IOP in eyes with NVG. ²

². Elmekawey H, Khafagy A. Intracameral Ranibizumab and Subsequent Mitomycin C Augmented Trabeculectomy in Neovascular Glaucoma. J Glaucoma 2013 Apr 29
Ex-PRESS™ shunt

Provides controlled flow of aqueous from AC into sub-conjunctival space


Ahmed Glaucoma Valve-NVG

THE AHMED GLAUCOMA VALVE IN NEOVASCULAR GLAUCOMA (AN AOS THESIS)

BY Peter A. Netland MD PhD

ABSTRACT

Purpose: To evaluate the results of Ahmed glaucoma valve surgery in neovascular glaucoma and control patients.

Methods: In this retrospective comparative study, we reviewed 76 eyes of 76 patients, comparing the surgical outcomes in control patients (N=38) to matched neovascular glaucoma patients (N=38). Success was defined as intraocular pressure (IOP) ≥ 16 mm Hg and ≤ 21 mm Hg, without further glaucoma surgery, and without loss of light perception.

Results: Average follow-up for control and neovascular glaucoma patients was 18.4 and 17.4 months, respectively (P = .558). At last follow-up, mean IOP was 16.2 ± 5.2 mm Hg and 15.5 ± 12.5 mm Hg (P = .115) in control and neovascular glaucoma patients, respectively. Life-table analysis showed a significantly lower success for neovascular glaucoma patients compared with controls (P = .0092), with success at 1 year of 89.2% and 73.1%, at 2 years of 81.8% and 61.9%, and at 5 years of 81.8% and 20.9% for control and neovascular glaucoma eyes, respectively. Cox proportional hazards regression analysis showed neovascular glaucoma as a risk factor for surgical failure (odds ratio, 5.38; 95% CI, 1.22-23.84, P = .027). Although IOP control and complications were comparable between the two groups, visual outcomes were worse in neovascular glaucoma patients, with 9 eyes (23.7%) with neovascular glaucoma compared with no controls losing light perception vision (P = .002). The majority with loss of vision (5 of 9) had successful control of IOP during the postoperative period.

Conclusion: Neovascular glaucoma patients have greater risk of surgical failure after Ahmed glaucoma valve surgery compared with controls. Despite improved mean IOP with drainage implants, visual outcomes may be poor, possibly due to progression of underlying disease.


Glucomat Drainage Device (GDD)-NVG

- Krupin valve reported 79% of eyes with NVG had a 67% success rate in controlling IOP (< 24 mm Hg)
- Molteno implant, 60 eyes with NVG achieved a satisfactory IOP (< 21 mm Hg).
- Combined with the need for vitrectomy, consideration of pars plana tube-shunt insertion may reduce anterior segment complications.


A

Glucomat Drainage Device (GDD)

Pars plana modified Baerveldt implant controls IOP in a medically acceptable range with less hypotony and greater preservation of visual acuity than CPC.

GDD-Complications

- Hypotony with associated complications, blockage of the tube, tube migration, conjunctival erosion, and corneal endothelial loss.
- High IOP with flat anterior chamber, pupillary block, and aqueous misdirection.
- Cataract formation and diplopia/strabismus is more common with Baerveldt GDD.
- A hypertensive phase related to fibrous capsule is common in Ahmed valves. ¹


Cyclo-destructive Procedures

Destruction of ciliary body for reduced production of aqueous
G-probe (1,500-2,000mW: duration 1.5 to 2.5 secs: 24-30 spos)

Future Directions

- Linking genetic phenotypes to understand why certain individuals progress to NVG.
- Understanding the alternate outflow / role of lymphatics and uveoscleral outflow.
- To understand and detect fibrovascular membrane in the early stages of NVG using high definition imaging as a screening tool.
- Evidence-based clinical trials to validate effectiveness and safety of new surgical procedures.
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What is the driving force behind anterior segment neovascularization?

Michaelson (1948) hypothesized the existence of a soluble growth factor responsible for ocular NV

Folkman (1971) hypothesized the existence of a vascular growth factor necessary for tumor growth

Vascular permeability factor (1983) discovered but could not be sequenced

Discovery of Vascular Endothelial Growth Factor (VEGF)

Two labs (Ferrara, Connelly) independently reported the discovery of soluble glycoprotein that promoted growth of vascular endothelial cells (1989).

Sequencing showed it to be identical to VPF.

Disclosure

Research support from
• Regeneron
• Allergan

Advisory Board
• Regeneron
• Allergan
• Boehringer-Ingelheim

I will discuss off-label drug use
VEGF is critical to most ocular angiogenesis: neovascularization & hyperpermeability

What Are the Underlying Pathophysiologic Processes?

Two major processes contribute to angiogenesis and blood retinal barrier breakdown:
1. Inflammation
2. Ischemia

Both upregulate VEGF

VEGF and Receptors

Angiogenesis is mediated by activation of VEGFR2

VEGF165 is most important isoform

VEGF and Receptors

Neuropilin-1 potentiates VEGF activation of VEGFR2


Current Ocular Anti-VEGF Drugs Bind Diffusible VEGF, Thereby Preventing Receptor Binding and Activation

Ramucirumab VEGFR2 blocker
Stomach cancer
Receptor tyrosine kinase inhibitors


VEGF is an Inflammatory Cytokine

Signs & symptoms of AC neovascularization:
- Pain
- Photophobia
- Decreased VA
- Dilated conj vessels
- AC cell and flare
- Iris NV
- Angle NV


Diagnosis of NVG

- Maintain a high index of suspicion.
- Ask about predisposing factors.
- Inflammatory signs may precede IOP elevation.

*** A work-up to determine etiology should not delay institution of therapy

“Time is nerve fiber layer.”

Management of NVG….
1. Find Responsible Etiology

- Consider ocular and systemic etiologies
- Workup and referrals as indicated.
- Do NOT let w/u delay initiation of therapy.

2. Pharmacologically lower IOP

Be very aggressive in lowering IOP… Throw everything at it but the…..

Don’t forget Diamox… best short-term IOP lowering drug…

Avoid Mannitol…if you need to immediately lower IOP…perform a paracentesis

3. Treat the neovascularization

1. Immediate Treatment
   a. anti-VEGF injections
      - bevacizumab (Avastin) is drug of choice
   b. Pan-retinal laser photocoagulation

2. Long-term Treatment
   a. Pan-retinal laser photocoagulation
   b. Pan-retinal cryoablation
   c. Consider vitrectomy/lensectomy if view precludes retinal ablation
**Binding Affinities of Anti-VEGF Drugs**

Drug-VEGF $\rightleftharpoons K_d$ Drug + VEGF

Binding affinity $\sim \frac{1}{Dissociation\ constant\ (K_d)}$

**Inhibition of endothelial cell migration and proliferation**

- **Bevacizumab**: $58 - 1,100\ pM$
- **Ranibizumab**: $46 - 192\ pM$
- **Aflibercept**: $0.5 - 1\ pM$


**Intravitreal Half-lives of Anti-VEGF Drugs**

- **Ranibizumab**: 48 kDa
- **Aflibercept**: 115 kDa
- **Bevacizumab**: 149 kDa

Log $t_{1/2} = -0.32 + 0.432 \log MW - 0.157 \log P + 0.003 \text{dose/solubility}$


- Bevacizumab: 9.8 days
- Aflibercept: 9.0 days (est.)
- Ranibizumab: 7.1 days

**Inject Early and Often**

Despite all the comparisons between the anti-VEGF drugs they work equally well in most patients for most problems. Since NVG is off-label for all drugs...bevacizumab is the cost-effective choice.

Who should give it?
- No reason that comp ophthalmologist can’t.

Limitations:
- experience
- level of comfort
- access to bevacizumab

**Retinal Ablation**

Usual duration of action of anti-VEGF is 4 weeks so laser can be:
1. performed immediately
2. performed electively

Pan-retinal cryoablation… relic from the past…
If media prevents timely laser…
Cataract extraction +/- vitrectomy
With intraoperative pan-retinal laser

4. Long-term control of IOP
1. Pharmacotherapy --- if control is adequate
2. Tube shunt surgery --- often required
3. Cyclocryo (or laser) ablation --- unusual

Conclusions
1. Evaluate and treat quickly
2. Control IOP pharmacologically
3. Block VEGF
4. Ablate ischemic tissue
5. Watch for long-term IOP elevation (common)

Thank You