Introduction to von Hippel Lindau Retinal Capillary Hemangioblastoma

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So What Parts of the Eye are Affected by VHL

- **Retina**
  - Neural tissue that senses light
  - Similar to film of a camera

- **Optic nerve**
  - Transmits visual information from the retina to the brain
Retina Anatomy
Juxtapapillary lesions (near optic nerve)

Near important structures

- Optic nerve
  - Transmits information to brain

- Macula (center of retina)
  - Used to see faces and read

Affect central vision

Harder to treat without treatment damage
How do we examine the Retina?

- Ophthalmoscopy
  - Clinical exam with special lenses

- Fluorescein angiography
  - Dye injection allows detailed evaluation of blood vessels
  - Abnormal blood vessels leak dye
  - New Wide Field Imaging

- Optical Coherence Tomography
  - Optical cross section
Ophthalmoscopy
Fluorescein Angiogram
Optical Coherence Tomography
Figure 51-19 Modified schematic drawing of a microscopic section of retina, pigment epithelium, and choroid.
Macular Anatomy

Figure 51-20 Modified schematic drawing of a microscopic section of the macula.
How do visual acuity (VA) scores impact your patients?¹,²

20/30 to 20/60
- Difficulty reading printed materials
- Need strong reading lenses, bifocals, or magnifiers to read normal-size print
- If best corrected VA falls below 20/40, an unrestricted driver’s license cannot be obtained in the majority of states

20/80 to 20/160
- Difficulty reading large-print materials, even with a magnifier
- Must rely on prescriptive low-vision optical and electronic devices for reading

20/200 to 20/400
- Extreme difficulties recognizing facial features and road signs
- Must rely on prescriptive low-vision optical and electronic devices for reading

Examples of RCH Lesions
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Incidence of VHL RCH and Visual Loss

- 37% of patients with VHL
  - From NIH series of >800 pts
- Only 1 of 18 was legally blind in both eyes
- But..
- 1 in 4 with RCH had monocular blindness
- 1 in 5 with RCH had enucleation
Reasons for Visual Loss

- Fluid leak from RCH
- Thickened retina
  - Cellular dysfunction
- Retinal detachment
  - Exudative
  - Tractional
- Location of lesions
  - Harder to treat if juxtapapillary
  - Risk of optic nerve injury from treatment
Treatment

- Large Randomized trials are lacking
- Most publications are small case series
Thermal Laser
Photodynamic Therapy
Cryotherapy
Intravitreal injection of anti-VEGF
Radiation
  External Beam
  Proton Beam
  Brachytherapy
Surgery
Thermal Laser

- Uses heat to ablate lesion
- Will only treat small lesions
- Can try feeder vessel treatment
  - Variable success
- Leaves Scarring
- Damages Retina or Optic Nerve
Several Small Lesions
Fluorescein Angiogram Guides Treatment
After Laser
Figure 51-46 Abnormal choroidal vessels: subretinal neovascularization.

A. Schematic view of the retina shows a small break in Bruch’s membrane, with a fine proliferation of capillaries through the break dissecting under and lifting up the pigment epithelium. There is a shallow sensory retinal detachment.

B. Color photograph of the left macula. There is a dirty-gray membrane involving the central macula. Note the small area of subretinal hemorrhage. There is a shallow sensory retinal detachment.

C. The arteriovenous-phase fluorescein angiogram shows fine, lacy, irregular hyperfluorescence corresponding to a small, fine patch of subretinal neovascularization.

D. Late-phase fluorescein angiogram shows leakage of these vessels into the subpigment epithelial and subretinal spaces. COMMENT: This patient had a small patch of subretinal neovascularization involving the central fovea. The angiogram shows typical, early vascular fluorescence (in a nodular, irregular, lace-like fashion) and late hyperfluorescent leakage.
Figure 51-46 Abnormal choroidal vessels: subretinal neovascularization. A, Schematic view of the retina shows a break in Bruch’s membrane, with a fine proliferation of capillaries through the break dissecting under and lifting up the pigment epithelium. There is a shallow sensory retinal detachment. B, Color photograph of the left macula. There is a dirty-gray membrane involving the central macula. Note the small area of subretinal hemorrhage. There is a shallow sensory retinal detachment. C, The arteriovenous-phase fluorescein angiogram shows fine, lacy, irregular hyperfluorescence corresponding to a small, fine patch of subretinal neovascularization. D, Late-phase fluorescein angiogram shows leakage of these vessels into the subpigment epithelial and subretinal spaces. COMMENT: This patient had a small patch of subretinal neovascularization involving the central fovea. The angiogram shows typical, early vascular fluorescence (in a nodular, irregular, lace-like fashion) and late hyperfluorescent leakage.
Figure 51-33 Choroidal occlusion secondary to laser photocoagulation. A. Left macula. Color photograph shows laser photocoagulation treatment of subfoveal subretinal neovascularization. B. The early arteriovenous-phase fluorescein angiogram of the left macula shows hypofluorescence of the macula and a large area temporally. The macula hypofluorescence corresponds to the laser treatment area which included area with retinal vessels and area with retinal vessels in the treated area. The large area of hypofluorescence temporally represents an area of choroidal occlusion secondary to the laser burn. C. Late phase fluorescein angiogram shows continued hypofluorescence of the area temporal to the macula and some early leakage from the retinal vessels in the laser treated area. D. Color photograph of the left macula four months later shows an atrophic laser burn with some hyperpigmentation. The pigment epithelium temporal to the macula appears normal. E. Laser lesion centrally shows hypofluorescence that is due partly to hyperpigmentation but mostly to closure of choriocapillaris and choroid. The area of previous occlusion temporal to this lesion now shows normal ground-glass choroidal fluorescence. F. Fluorescein angiogram temporal to the left macula shows normal choriocapillaris filling. COMMENT: This patient had laser treatment of an area of subfoveal subretinal neovascularization. The laser burn caused closure of the choroid in the area of the burn as well as temporary closure of choroidal vessels temporally. Short posterior ciliary arteries and choroidal arteries from the area of the laser burn to the area temporal must have been obstructed by the laser but later reopened. The overlying pigment epithelium temporal to the laser lesion was not affected by the choroidal closure.
Figure 51-33 Choroidal occlusion secondary to laser photocoagulation. A, Left macula. Color photograph shows laser photocoagulation treatment of subfoveal subretinal neovascularization. B, The early arteriovenous-phase fluorescein angiogram of the left macula shows hypofluorescence of the macula and a large area temporally. The macula hypofluorescence corresponds to the laser treated area and includes the overlying retinal vessels, which are obliterated by the laser burn. The large area of hypofluorescence temporally represents an area of choroidal occlusion secondary to the laser burn. C, Late-phase fluorescein angiogram shows continued hypofluorescence of the area temporal to the macula and some early leakage from the retinal vessels in the laser treated area. D, Color photograph of the left macula four months later shows an atrophic laser burn with some hyperpigmentation. The pigment epithelium temporal to the macula appears normal. E, Laser lesion centrally shows hypofluorescence that is due partly to hyperpigmentation but mostly to closure of choriocapillaris and choroid. The area of previous occlusion temporal to this lesion now shows normal ground-glass choroidal fluorescence. F, Fluorescein angiogram temporal to the left macula shows normal choriocapillaris filling. COMMENT: This patient had laser treatment of an area of subfoveal subretinal neovascularization. The laser burn caused closure of the choroid in the area of the burn as well as temporary closure of choroidal vessels temporally. Short posterior ciliary arteries and choroidal arteries from the area of the laser burn to the area temporal must have been obstructed by the laser but later reopened. The overlying pigment epithelium temporal to the laser lesion was not affected by the choroidal closure.
Verteporfin dye infused
Dye is activated with laser light
‘Cold’ laser does not damage retina
Oxidative cascade ensues
Causing damage to blood vessel walls and thrombosis
Photodynamic Therapy and RCH

- Multiple case reports
- Sachdeva 2010
  - 50% (3/6) eyes stabilized or improved with PDT
Cryotherapy

- Freezes tissue using external probe
- Can treat thick lesions
- Uncomfortable
  - All eye coats are frozen, not just retina
Laser, PDT and Cryo leave scarring
Molecules that inhibit blood vessels grow may be better
Works downstream of HIF
Injected into Vitreous (clinic procedure)
The angiogenic cascade is a complex process\(^1-^3\)

VEGF-A is a member of a family of growth factors\textsuperscript{1,2}

- VEGF-A is a member of a family of growth factors that includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and PIGF\textsuperscript{*}

- VEGF-A is a homodimeric glycoprotein secreted by a variety of cells

- The “receptor-binding domain” of VEGF-A is essential for this receptor–VEGF-A interaction and its role in triggering angiogenesis

- VEGF-A initiates the angiogenic cascade by binding to VEGF receptors on the surface of endothelial cells

\textsuperscript{*}Placental growth factor.

LUCENTIS development

Full-length monoclonal antibody

Fc
The Fc portion on full-length antibodies may contribute to longer half-life

Antibody fragment: FAb* (LUCENTIS)

Achieves rapid systemic elimination

*The 5 spheres indicate the position of the amino acid changes in the structure of LUCENTIS compared with the full-length monoclonal antibody. A sixth amino acid change, introduced for cloning purposes in the constant domain of the heavy chain, is not represented.
AntiVEGF

- Conflicting reports of success
- Wang 2008 ranibizumab
  - Avg 10 monthly injections
  - Mean loss of 2 lines of vision
- Hrisomalos 2010 bevacizumab
  - 60 monthly treatments
  - Vision improved 5 lines
Radioactivity
Radiation

External Beam
- Reports of success even for juxtapapillary lesions
  - Matsuo 2011
- Risk of radiation retinopathy

Brachytherapy
- Risk of radiation
- Limitation if near nerve
Proton Beam for juxtapapillary lesions

- Seibel 2014
- 8 eyes
- Exudation resolved
- Vision did not improve

Should have less ‘run off’ side effect
Surgery

- For complex, advanced cases
- Surgical removal of scar
- Removal of blind/painful eye

Better to avoid need for surgery
Treatment strategy

- Screen frequently
- Screen with Fluorescein Angiography
- Treat Early
- Smaller lesions are easier to treat
- Better Outcome
Screening: Small Lesion
Small Lesion
After Laser
1 Year After Laser
Screening
Screening: Utility of Fluorescein
Genetics

- Prevalence of RCH lesions
  - Amino acid substitution
    - 37%
  - Protein truncation
    - 40%
  - Complete deletion
    - 14%

- Juxta papillary lesions
  - More common with protein truncations
Genetics: Missense mutation

- Alpha domain v beta domain
  - 46% v 34% prevalence

- Alpha
  - 90% had peripheral lesions
  - 15% had juxtapapillary lesions

- Beta
  - 77% had peripheral lesions
  - 36% had juxtapapillary lesions