Ophthalmologic Issues in VHL

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VHL Disease

- Autosomal dominant neoplastic disorder
- Multiple benign or malignant tumors and cysts
  - CNS (brain, spinal cord, retina, inner ear)
  - visceral organs (kidney, adrenal gland, pancreas, epididymis)
- Rare disorder (1:36,000 live births)
- Penetrance over 90% by 65 years of age

A Brief History of VHL Disease

- von Hippel (1904)
  - retinal capillary hemangioblastomas
  - several generations of family members
  - several pedigrees
- Lindau (1926)
  - observed familial syndrome
    - hemangioblastomas (retina and cerebellum)
    - cysts (kidney, pancreas, epididymis)
- Melmon and Rosen (1965)
  - criteria for clinical diagnosis

Ocular Manifestations
Retinal Capillary Hemangioblastoma

- May be the first manifestation of VHL disease
- Range from tiny lesions to large tumors with major visual impairment
- Located predominantly in retinal periphery (85%)
- Initial appearance
  - subtle red or gray dot
- With growth, appears as distinct nodule
  - dilated feeding and draining vessels

Ocular Manifestations
Optic Nerve Capillary Hemangioblastoma

- May occur on or immediately adjacent to optic disc
- Occasionally difficult to recognize
  - feeding/draining vessels less prominent

Retinal & Optic Nerve Hemangioblastoma
Natural History

- Can appear at any age
  - patients typically have no symptoms initially
  - often discovered on routine or screening exam
- Without treatment
  - rarely regress spontaneously
  - usually grow slowly and progressively
  - often begin leaking as they enlarge
  - eventually displace normal structures
  - may completely fill the eye

Retinal & Optic Nerve Hemangioblastoma
Natural History/Secondary Complications

- Leakage
  - retinal edema (swelling)
  - lipid (yellow) exudates
- Fibrosis (scar tissue)
- Retinal detachment
  - exudative (from leakage)
  - tractional (from fibrosis and vitreous traction)
- Bleeding
- Neovascular glaucoma

Diagnosis
Ocular Hemangioblastoma

- Diagnosis typically based on clinical appearance
- No definitive diagnostic tool
- Confirmatory/useful studies
  - wide-angle fundus photography
  - fluorescein angiography
  - ultrasonography
  - optical coherence tomography
    - detection of associated macular edema

Diagnosis
VHL Disease

CLINICAL CRITERIA	
Family History +	CNS* hemangiobastoma, Pheochromocytoma, *or* Clear cell renal carcinoma
Family History -	2 or more CNS hemangioblastomas *or* CNS hemangioblastoma + visceral tumor

- Up to 20% of cases arise de novo (first affected member of family)--genetic testing extremely helpful in such patients
- Regular clinical screening studies recommended for family members with mutations
  - ophthalmoscopy yearly starting in infancy

* *CNS includes retina*

Epidemiology
Ocular Manifestations

- **Large NEI study** *(Wong WT, et al, 2008)*
  - 38% of patients had ocular involvement
    - mean age 36 years (range, 7 to 84)
    - 47% male
    - 95% white
  - laterality
    - 42% unilateral
    - 58% bilateral
  - location
    - 85% peripheral
    - 15% optic nerve

Vision Loss in VHL
Prevalence

- NEI study
  - 77% had 20/20 vision
  - 5.7% legally blind
  - 20% had visual impairment in one eye

Vision Loss in VHL
Causes

- Tumor exudation (leakage)
  - macular edema
  - exudative retinal detachment
- Glial proliferation (scar tissue)
  - retinal distortion
  - traction retinal detachment
- Neovascularization
  - vitreous hemorrhage or retinal traction
  - neovascular glaucoma
- Neurological lesions
  - increased intracranial pressure leading to optic atrophy
  - hemangioblastomas affecting RB optic nerve or optic tract

Ablative Treatment
Retinal Hemangioblastomas

Lesion size / location	Treatment modality
Very small (1-2 mm)	Laser (direct)
Small (3-5 mm)	Laser (feeder vessel + direct)
Small, very peripheral	Cryotherapy
Moderate to large (> 5 mm)	Cryotherapy (consider adjunctive steroid or anti-VEGF)
Complicated (traction, retinal detachment, vitreous hemorrhage)	Vitrectomy and/or scleral buckling surgery (with laser, diathermy and/or cryotherapy)

The smaller the lesion, the easier and safer it is to treat

Ablative Treatment
Optic Nerve Hemangioblastomas

- *Treatment difficult—no consensus*
  - Laser treatment
    - risk of visual acuity and/or visual field loss
    - serial, low-intensity treatments promising
  - Photodynamic therapy
    - mixed results
    - risk of optic nerve injury
  - Transpupillary thermotherapy
    - risk of significant nerve injury (little data)
  - Radiation
    - should be avoided (increases VEGF production)

Pharmacologic Treatment
Anti-Angiogenic Agents

- VHL involves high levels of vascular endothelial growth factor (VEGF)
  - drives tumor growth and vessel leakage
- Anti-VEGF treatment is rational approach
- Studies to date
  - decreased leakage
  - no change in tumor size
  - anti-VEGF treatment alone appear inadequate
- Successful pharmacologic approaches may need to target multiple proteins upregulated in VHL