INTRODUCTION TO VHL

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OBJECTIVES

• Become familiar with the history of VHL
• Understand the genetics of VHL
• Recognize features of VHL
• Learn how VHL is diagnosed
• Become familiar with current screening recommendations
• Learn about the IU Health Hereditary Renal Disease Clinic
WHAT IS VHL?

• von Hippel-Lindau (VHL) disease is a hereditary cancer syndrome that increases one’s risk for several types of tumors

• Features of the condition can occur in childhood, adolescence or adulthood

• Hemangioblastomas of the brain, spinal cord and retina are characteristic features
1 in 36,000 people
HISTORY OF VHL

• Eugene von Hippel first described tumors of the eye in 1904

• Arvid Lindau described tumors of the brain and spine in 1927
GENETICS OF VHL

- VHL gene
- Autosomal dominant pattern
  - Inherited- 80%
  - De novo 20%
- Different subtypes of VHL depending on gene mutation
Normal Karyotype
Autosomal Dominant

Parents

Children

80%

Autosomal Dominant - New Mutation

Parents

Children

20%

sporadic mutation occurs during formation of egg or sperm cell or during embryonic development.
VHL

**Low risk**

- TYPE 1
  - Hemangioblastomas
  - Kidney Cancer
  - deletions, insertions, truncations and missense mutations

**High risk**

- Pheochromocytoma

**TYPE 2A**
- Hemangioblastomas
- Pheochromocytomas
- Pancreatic tumors
- missense mutations

**TYPE 2B**
- Hemangioblastomas
- Kidney Cancer
- Pheochromocytomas
- Pancreatic tumors
- missense mutations

**TYPE 2C**
- Pheochromocytomas only
- missense mutations
CLINICAL MANIFESTATIONS

Brain hemangioblastomas - 44-72%
Spinal cord hemangioblastomas - 13-50%

Retinal angiomas - 25-60%
Endolymphatic sac tumors - 10-25%

Lung hemangioblastomas

Liver hemangioblastomas - 7%

Pancreatic tumor or cysts - 35-70%

Epididymal cystadenomas - 25-60%

Pheochromocytoma - 10-20%
Kidney Cancer - 25-60%
Kidney cysts
Kidney hemangioblastoma

Broad ligament cystadenomas - 10%
WHAT ARE FEATURES OF VHL?

• Hemangioblastomas
  • Retinal – 12-25 yrs
  • Brain- 18-35 years
  • Spinal cord- 24-35 years

• Pancreatic lesions- 24-35 years
  • Cysts
  • Pancreatic neuroendocrine tumors

• Endolymphatic sac tumors- 24-35 years

• Kidney lesions- 25-50 years
  • Cysts
  • Kidney cancer- typically clear cell
WHAT ARE FEATURES OF VHL?

• Pheochromocytomas-12-25 years
  • Majority are benign

• Epididymal cystadenomas- 14-40 years
  • Benign but may cause pain
  • If bilateral, may cause infertility

• Broad ligament cystadenomas- 16-46 years
  • Benign but may cause pain
WHEN TO REFER?

• Family history of VHL

• Individuals with any of the following:
  • Hemangioblastoma (retina, brain or spine)
  • Pheochromocytoma
  • Kidney cancer <45 years old
  • Multiple kidney and pancreatic cysts
  • Pancreatic neuroendocrine tumors
  • Endolymphatic sac tumors
  • Multiple papillary cystadenomas of the epididymis or broad ligament
HOW IS VHL DIAGNOSED?

• Simplex case (no family history) includes the presence of 2 or more features:
  • ≥2 hemangioblastomas (retina, brain or spine) or 1 hemangioblastoma and multiple kidney or pancreatic cysts
  • kidney cancer
  • pheochromocytoma
  • endolymphatic sac tumors, cystadenomas of the epididymis or broad ligament or PNET

• Individual with family history plus 1 or more features:
  • spinal, retinal or brain hemangioblastoma
  • pheochromocytoma
  • kidney cancer
  • multiple kidney and pancreatic cysts
## WHAT ARE SCREENING RECOMMENDATIONS?

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<tr>
<th>Age</th>
<th>Screening</th>
<th>Frequency</th>
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| Beginning at age 1 year | - physical exam with evaluation for neurological symptoms, hearing loss and blood pressure  
                           - eye evaluation with indirect ophthalmoscope | Annually, Annually |
| Beginning at age 5 years | - plasma or 24-hr urine for fractionated metanephrines  
                           - hearing assessment                                             | Annually, Every 2-3 years |
| Beginning at age 8 years | - abdominal ultrasound                                                    | Annually       |
| Beginning at age 16 years | - MRI of the brain, spine and abdomen                                     | Every 2 years   |
HEREDITARY CANCER SYNDROMES

- Von Hippel-Lindau
- Tuberous Sclerosis Complex
- Hereditary Leiomyomatosis Renal Cell Carcinoma

- Birt-Hogg-Dubé

- 62%
- 19%
- 15%
- 4%