VHL 101: AN INTRODUCTION

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LEARNING OBJECTIVES

• What is von Hippel–Lindau (VHL) disease?
• What are the clinical manifestations of VHL disease?
• How is VHL disease diagnosed?
• What is the VHL gene and what does it do?
• How is VHL related to renal cell carcinoma?
• What is the screening protocol for VHL disease?
• What is von Hippel–Lindau (VHL) disease?
• What are the clinical manifestations of VHL disease?
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WHAT IS VHL DISEASE?

• Inherited, autosomal dominant condition that occurs in 1:36,000 people

• Results from a germline mutation in \textit{VHL}, a tumor suppressor gene

• 20\% cases arise from \textit{de novo} mutations in patients without family history of VHL disease

AUTOSOMAL DOMINANT INHERITANCE

- Has VHL mutation
- No VHL mutation

Ambry Genetics
What is VHL disease?

• Higher risk of non-cancerous and cancerous tumors.

• Non-Cancerous Tumors:
  • Renal, pancreatic, and epididymal cysts
  • Central nervous system hemangioblastomas
  • Retinal hemangioblastomas
  • Endolymphatic sac tumors (ELSTs).

• Cancerous Tumors:
  • Kidney cancer/renal cell carcinoma (RCC)
  • Pheochromocytoma (PCC)
  • Neuroendocrine tumors of the pancreas (PNET)

Two classifications of VHL Disease:

- **Type 1 VHL Disease** - low risk PCC
  - High risk of hemangioblastoma
  - High risk of RCC

- **Type 2 VHL Disease** - high risk PCC
  - Type 2A: Hemangioblastoma and pancreatic tumors; low risk of RCC
  - Type 2B: Hemangioblastoma and pancreatic tumors; high risk of RCC
  - Type 2C: Pheochromocytoma only

Cohen and McGovern. NEJM 2005;353:2477-2490
WHO WERE VON HIPPEL AND LINDAU?

- **Eugen von Hippel (1867-1939)**
  - German ophthalmologist
  - Reported hereditary retinal angiomatosis in 1911

- **Arvid Lindau (1892-1958)**
  - Swedish pathologist
  - Recognized the link between VHL retinal lesions and cerebellar hemangioblastomas in 1926
  - Also described renal tumors and cysts

- The term von Hippel-Lindau disease was first used in 1936

LEARNING OBJECTIVES

• What is von Hippel–Lindau (VHL) disease?

• **What are the clinical manifestations of VHL disease?**

• How is VHL disease diagnosed?

• What is the *VHL* gene and what does it do?

• How is *VHL* related to renal cell carcinoma?

• What is the screening protocol for VHL disease?
CLINICAL MANIFESTATIONS OF VHL DISEASE

- Retinal haemangiomas (70%)
- CNS haemangioblastomas (60-84%)
- Endolymphatic sac tumours of the middle ear (14%)
- Lung cysts (rare, <1%)
- Pheochromocytomas (18%)
- Pancreas: cysts (70%), serous cystadenomas (9%), neuroendocrine tumours (9%)
- Kidney: cysts (66%), clear cell renal cell carcinomas (69%)
- Epididymal (male, 54%) or broad ligament (female) papillary cystadenomas

Central nervous system

**Hemangioblastomas**

- **Cardinal feature of VHL disease**
  - Presenting feature of VHL in ~ 40% of patients

- **Occurs in 60-80% of patients with VHL disease**

- **Due to germline mutation, can develop before birth and are diagnosed early, often under 10 years**

- **Most common in cerebellum, spinal cord, and brainstem**


Ben-Skowronek et al, Horm Res Paediatr 2015;84:145–152

Wikipedia (picture), accessed 10/12/18
CENTRAL NERVOUS SYSTEM HEMANGIOBLASTOMAS

- Can enlarge over time, but are typically benign tumors (not cancerous)
- Main treatment is usually surgical resection
- Gamma knife/stereotactic radiotherapy may be an option if surgically not resectable or as a salvage therapy
- Important cause of physical disability in VHL patients

Butman et al, JAMA 2008; 300: 1334–1342
Wikipedia (picture), accessed 10/12/18
Central Nervous System
Hemangioblastomas

Symptoms are related to mass effect

- Increased intracranial pressure
  - Headaches
  - Dizziness
- Limb or truncal ataxia
  - Weakness
  - Pain in arms and legs
  - Back pain
  - Numbness

Ben-Skowronek et al, Horm Res Paediatr 2015;84:145–152
RETINAL CAPILLARY HEMANGIOBLASTOMAS

- Same process as CNS hemangioblastomas and similarly can present < 10 years age
- Most common presenting feature of VHL disease (50-60%)
- Bilateral in ~ 50% of cases
- Visual loss is the main complication
  - Cumulative risk of visual loss ~ 35%

RETINAL CAPILLARY HEMANGIOBLASTOMAS

• Diagnosed by ophthalmologic examination and retinal angiography if needed

• Main treatments include laser photocoagulation or cryotherapy
  • Small tumors: argon laser photocoagulation
  • Larger or peripheral tumors: cryotherapy

• Anti-angiogenic therapies are under investigation

CLEAR CELL RENAL CELL CARCINOMAS

- Most frequent *malignant* tumor in VHL disease
- Risk of RCC is highest for Type 1 and Type 2B VHL disease where lifetime risk of ~ 70%
- Mean age at diagnosis of RCC is ~ 40 years
- High risk of multiple and bilateral RCC

Cohen and McGovern.  NEJM 2005;353:2477-90
CLEAR CELL RENAL CELL CARCINOMAS

- Multiple renal cysts and carcinomas are common in VHL disease (30-60%)

- Optimum treatment is a nephron-sparing approach
  - Many RCC tumors are detected during routine screening
  - Usually do not require immediate intervention (grow slowly)
  - Almost no metastatic potential < 3cm
  - RCC ≥ 3 cm have a 25% risk of developing metastatic disease
    - Treated with partial nephrectomy or radiofrequency ablation

• Common in all Type 2 VHL disease

• Mean age of diagnosis of pheochromocytoma is ~ 30 years

• Overall risk of malignancy in VHL-associated pheochromocytoma is ~ 2.5-5%

• Lower than the risk for malignancy in standard pheochromocytoma (~10%)

Ben-Skowronek et al, Horm Res Paediatr 2015;84:145–152
Urologyspecialist.com.au (picture), accessed 10/12/18
PHEOCHROMOCYTOMAS

• Symptoms due to too much adrenaline:
  • Headaches, drenching sweats, anxiety and agitation
  • Cardiac complications: heart attack, stroke, heart palpitations, heart failure

• Treatment is surgical resection.

Ben-Skowronek et al, Horm Res Paediatr 2015;84:145–152
Pancreatic islet tumors

- Pancreatic cysts and tumors are common in VHL disease
- Pancreatic neuroendocrine tumors (PNETs) occur in 12-17% of patients with VHL
- Due to malignant/metastatic potential, surgery is recommended for solid tumors > 3 cm and tumor doubling time < 500 days

Blansfield et al, Surgery 2007; 142: 814–818;discussion 818.e1–2
Corcos et al, Pancreas 2008; 37: 85–93
**ENDOLYMPHATIC SAC TUMORS (ELST)**

- Occurs in up to 11% of VHL patients; mean age 22 years
- Tumors arising from endolymphatic sac (normally involved with inner ear fluid homeostasis)
  - Can invade into bone in the skull and can grow into nerves
- Most ELST are sporadic; only 1 in 5 are related to VHL
- Bilateral ELSTs are pathognomonic for VHL disease
- Symptoms are hearing loss, tinnitus, vertigo, ear fullness
- Treatment is early surgical resection

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HOW IS VHL DISEASE DIAGNOSED?

• Diagnosis of VHL disease is made based solely on characteristic clinical features:
  • One index tumor (hemangioblastoma, pheochromocytoma, RCC) AND a positive family history
  • Two or more CNS hemangioblastomas
  • One CNS hemangioblastoma with one visceral manifestation

• Genetic testing to establish/confirm the definite diagnosis is indicated for all patients with suspected VHL disease
  • Blood test
  • Buccal (cheek) swab

Schmid et al, Oncol Res Treat 2014;37:761–771
• Any blood relative of an individual diagnosed with VHL disease

• Individuals with one VHL-associated lesion AND a positive family history of VHL-associated lesions

• Individuals with TWO VHL-associated lesions
Individuals with ANY of the following:

- RCC diagnosed < 40 years
- Bilateral or multiple cRCC
- RCC with positive family history
- Hemangioblastoma diagnosed < 30 years
- > 2 CNS hemangioblastomas
- Hemangioblastoma PLUS RCC or PCC or PNET
MASSACHUSETTS GENERAL HOSPITAL
CRITERIA FOR REFERRAL TO VHL CLINIC

Individuals with ANY of the following:

• Pheochromocytoma diagnosed < 40 years

• Bilateral or multiple pheochromocytomas

• Pheochromocytoma and positive family history

• > 1 pancreatic serous cystadenomas

• > 1 pancreatic neuroendocrine tumors

• Multiple pancreatic cysts plus any VHL-associated lesion
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WHAT IS THE VHL GENE AND WHAT DOES IT DO?

• *VHL* gene is located on the short arm of chromosome 3

• Everyone has two copies of the *VHL* gene

• *VHL* mutation is inherited in an autosomal dominant fashion: 50/50 chance

• *VHL* normally functions as a tumor suppressor gene and helps with normal breakdown of proteins called HIF (hypoxia inducible factor)

Cohen and McGovern. NEJM 2005;353:2477-90
Ambry Genetics
HOW IS VHL RELATED TO RENAL CELL CARCINOMA?

- When *VHL* is normal, hypoxia proteins (HIF) get degraded.
- When *VHL* is mutated, hypoxia proteins do not get degraded and they turn on other proteins (VEGF, PDGF, TGF) that then stimulate growth and development of kidney cancer.

Schmid et al, Oncol Res Treat 2014;37:761–771
Cohen and McGovern. NEJM 2005;353:2477-90
VHL biology helped develop treatments for RCC.

- **1992**: Interleukin-2
- **1996**: Sorafenib
- **2000**: Sunitinib
- **2004**: Temsirolimus
- **2008**: Everolimus
- **2012**: Bevacizumab + IFN, Pazopanib
- **2016**: Axitinib
- **2018**: Cabozantinib, Lenvatinib + Everolimus
- **2018**: Nivolumab & Ipilimumab
CLINICAL TRIALS FOR VHL-RELATED RCC

• Blood vessel-targeting drugs:
  • Pazopanib
  • Axitinib
  • Cabozantinib

• HIF-targeting drug:
  • PT2977 (Peloton Therapeutics)
  • Open at NIH, Mass General, MDACC, other locations
  • Opening at University of Colorado in November 2018
  • ClinicalTrials.gov Identifier: NCT03401788
    • Contact information for each study site
A Phase 2 Study of PT2977 for the Treatment of Von Hippel Lindau Disease-Associated Renal Cell Carcinoma

Inclusion Criteria:

- Has a diagnosis of von Hippel Lindau disease, based on a germline VHL alteration
- Has at least 1 measurable solid RCC tumor and no RCC tumor that requires immediate surgical intervention. The diagnosis of RCC can be radiologic (histologic diagnosis not required). Patients may have VHL disease-associated tumors in other organ systems

Exclusion Criteria:

- Has received prior treatment with PT2977 or another HIF-2α inhibitor
- Has had any systemic anti-cancer therapy (includes anti-VEGF therapy or any systemic investigational anti-cancer agent)
- Has an immediate need for surgical intervention for tumor treatment
- Has evidence of metastatic disease on screening imaging
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What is the screening protocol for VHL disease?

- Affected VHL individuals should undergo a surveillance program
- At risk relatives of VHL patients should undergo a comprehensive screening program beginning in childhood
  - Unless ruled out by genetic testing

Ben-Skowronek et al, Horm Res Paediatr 2015;84:145–152
Schmid et al, Oncol Res Treat 2014;37:761–771
What is the screening protocol for VHL disease?

- **Screening for CNS hemangioblastoma**
  - MRI scans of the head (±spine) every 12-36 months beginning the first year of life in children with genetically diagnosed VHL syndrome, especially in adolescents.

- **Screening for retinal capillary hemangioblastoma**
  - Ophthalmic examinations every 12 months beginning in infancy or early childhood.

Ben-Skowronek et al, Horm Res Paediatr 2015;84:145–152
Schmid et al, Oncol Res Treat 2014;37:761–771
WHAT IS THE SCREENING PROTOCOL FOR VHL DISEASE?

• Screening for renal cell carcinoma
  • Ultrasound or MRI scans of the abdomen every 12 months from age 16 years.

• Screening for pheochromocytoma
  • Blood pressure monitoring
  • Yearly screening with urine tests and blood tests for pheochromocytoma beginning in early childhood from age 8 years
  • MRI screening for RCC can also be used for screening for pheochromocytoma

Ben-Skowronek et al, Horm Res Paediatr 2015;84:145–152
Schmid et al, Oncol Res Treat 2014;37:761–771
CONCLUSIONS

• VHL disease is a highly complex multisystem disorder that requires input from many different medical specialties.

• Coordination with and input from patients and their families are essential.

• Early diagnosis of VHL complications improves prognosis
  • Affected VHL individuals should undergo surveillance
  • At risk relatives of VHL patients should undergo a comprehensive screening program beginning in childhood (unless ruled out by genetic testing)