

## Renal Cell Carcinoma and VHL Disease

David Shure, MD  
September 15, 2009

## Overview

- Sensorineural hearing loss DD
- Pendred Syndrome
- RCC
- VHL dz/ protein as TSG
- HIF-1
- Endolymphatic Sac Tumors
- VHL Family Alliance
- Surveillance Protocols

## SSNHL: DD



- VHL: Bilat endolymphatic sac tumors
- Pendred Syndrome
- Viral Cochleitis: HSV, parainfluenza, influenza, mumps, measles
- Drugs: aminoglycosides, vancomycin, erythromycin, loop diuretics, cisplatin, antimalarials
- Neoplasm: acoustic neuroma, meningeal carcinomatosis, lymphoma, leukemia, plasma cell dyscrasias
- AI Dz: SLE, APLA, RA, Sjogrens, vasculitides, temporal arteritis
- Vascular: CVA, TIA
- Other: Menieres dz, Paget Dz, MS

## Pendred Syndrome



- First described in 1896
- Phenotype: coexistence of deafness and goiter
- 1996 syndrome mapped to chromosome 7
- Gene: PDS codes for a 780 aa protein ie pendrin, functions as an ion transporter
- Autosomal-recessive
  - Deafness and goiter
  - Gene isolated (PDS), protein: pendrin
  - mutation in a transport protein ("pendrin") on chromosome 7q, which transports iodide into the exocytotic vesicles in which thyroid hormone is synthesized



## Pendred Syndrome

- Radiology – CT/MRI temporal bone
  - Enlargement of endolymphatic system, most readily detected by documenting an enlarged vestibular aqueduct
    - Subset: have a Mondini defect, a malformation in which the cochlear turns are replaced by a single cavity or a rudimentary cochlea
    - Perchlorate test: determines whether iodide is normally organified into thyroglobulin, permits determination whether EVA pts might have Pendred syn.
    - Under conditions of sufficient nutritional iodide, most individuals with Pendred are clinically and biochemically euthyroid.

## Pendred Syndrome

- Radiology – CT/MRI temporal bone
  - Enlargement of endolymphatic system, most readily detected by documenting an enlarged vestibular aqueduct
    - Subset: have a Mondini defect, a malformation in which the cochlear turns are replaced by a single cavity or a rudimentary cochlea
    - Perchlorate test: determines whether iodide is normally organified into thyroglobulin, permits determination whether EVA pts might have Pendred syn.
    - Under conditions of sufficient nutritional iodide, most individuals with Pendred are clinically and biochemically euthyroid.

## Mondini Defect

- CT Temporal Bone
  - Black Arrow: sac-like cochlea
  - White arrow: amorphous vestibule without defined semicircular canals.



## Pendrin in the Kidney

- Pendred synd caused by homozygous or heterozygous mutations in SLC26A4 gene, encodes pendrin.
  - SLC26A4 mRNA expression abundant in renal cortex and cortical collecting duct localized to the apical brush-border membrane in type b intercalated cells.
  - Studies in human embryonic kidney cells show pendrin can exchange Cl with HCO<sub>3</sub>.
  - Pts with Pendred syn have no apparent abnl in acid-base metabolism, due to presence of other cl/ base exchangers.
  - SLC26a4 knockout mice have impaired ability to retain Na during dietary salt restriction 2/2 reduced abundance of ENAC. May contribute to regulation of bp and arterial pH through regulation of net acid and cl excretion. Potential target in HTN rx.

## Renal Cell Carcinoma

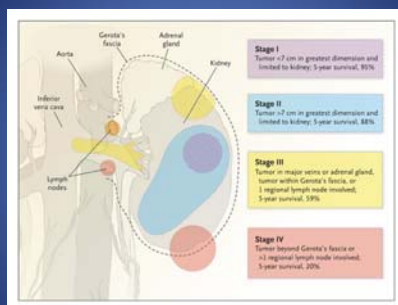


- Stats
  - 7<sup>th</sup> leading malignant condition in US among men and 12<sup>th</sup> women
  - Accts for 2.6% of all cancers
  - ~2% cases of renal cancer assoc with inherited syndromes
  - Discovered earlier widespread radiographic testing
  - 2005: 36,160 new cases, 12,660 deaths
  - 2009: 49,000 new cases, 11,000 deaths
  - RCC arise from renal epithelium acct for ~85% renal cancers
  - ¼ pts present with advanced dz
  - 1/3 pt's undergoing local resection have recurrence
  - Median survival for pts with metastatic dz ~13 mths

## Clinical Presentation

- Triad: flank pain, hematuria, palpable abd mass
- >50% dx incidentally via radiography
- RF: smoking, obesity, HTN, acquired cystic kidney dz
- 1.6: 1.0 M:F, peak incidence 6<sup>th</sup> and 7<sup>th</sup> decade
- Gross/ Microscopic hematuria

### Staging Overview and Five-Year Survival Rates for Renal Cancer



Cohen H and McGovern F. N Engl J Med 2005;353:2477-2490



## Von Hippel-Lindau

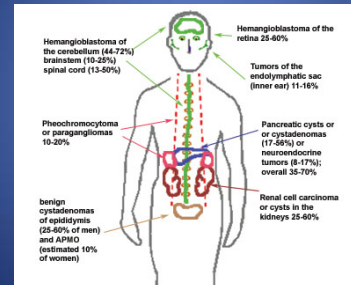
- Familial AD cancer syndrome
- Results from germ-line mutation in VHL gene on chromosome 3
- Rare 1: 39,000; initial manifestations occur at mean age ~26
- The VHL gene is in the region 3p25-p26, near the tip of the short arm of chromosome 3.



## VHL Hx

- Dr. Eugene von Hippel, Ger. ophthalmologist, described angiomas in the eye in 1893-1911.
  - Name originally only used in assoc with VHL in retina.
- Dr. Arvid Lindau, Swedish pathologist, 1<sup>st</sup> described angiomas of cerebellum and spine in 1926. Some of whom had retinal angiomas.
  - Both physicians were describing the same d/o.

## Spectrum of Tumors



## Clinical Review – Clinical Spectrum

- Maher, et al 1990 QJ Med
  - 152 pts with VHL
    - RCCs present significantly later than cerebellar hemangioblastomas or retinal angiomas
    - Among pts who survived to age 60, est probab of developing RCC, retinal angiomas, and cerebellar hemangioblastomas 69, 70, 84%
    - Median pt survival 49 yrs
    - Most deaths 2/2 RCC

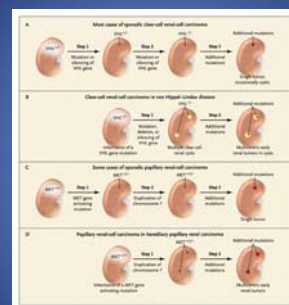
## RCC in VHL

- High risk for multiple renal cysts and RCC
- Occurs in 2/3 pts
- All VHL assoc RCCs are clear cell tumors
- Incr risk for RCC with age
- Multicentric and bilateral, arise in conjunction with cysts or de novo from non-cystic renal parenchyma
- Cysts in VHL represent a premalignant lesion
- Surveillance protocols

## Tumor Suppressor Gene (VHL)

- VHL protein, product of VHL gene is a TSG ID'd in 1993
  - One VHL allele is inherited with a mutation
  - Focal lesions ie RCC, arise from inactivation or silencing of remaining wild-type allele
  - Hypoxia-inducible genes are normally inhibited by VHL protein, incl sev encoding proteins involved in angiogenesis eg VEGF, TGF- $\alpha$ , GLUT-1. When VHL protein is lost, these proteins are over expressed, creating a microenvironment favorable for epithelial cell proliferation.
  - ie cells deficient in VHL protein behave as if they are hypoxic, even in conditions of normoxia

## Steps in the Development of Renal-Cell Carcinoma



Cohen H and McGovern F. N Engl J Med 2005;353:2477-2490

## Two Hit Model



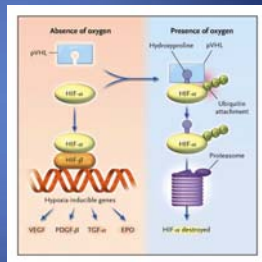
- First Hit: germline mutation inactivates one copy of the VHL gene in all cells
- Second hit: loss of expression of the second, normal allele, through either somatic mutation or deletion of the second allele

- *‘A fundamental challenge underlying much of the physiology and anatomy of higher organisms is avoiding local oxygen starvation. The efficiency with which we meet this challenge means that it is easy to take it for granted’*

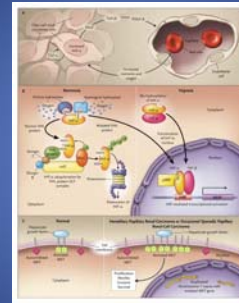
Patrick Maxwell, *HIF-1: An Oxygen Response System with Spatial Relevance to the Kidney*, JASN 2003

## Hypoxia Inducible Factor-1

- A major protein regulated by pVHL
- Composed of alpha/beta subunits, alpha subunit is sensitive to oxygen levels and is a substrate for pVHL protein complex
- In presence of normal O<sub>2</sub> tension, HIF1 $\alpha$  is enzymatically hydroxylated
- Hydroxylated HIF1 $\alpha$  subunit is bound by VHL protein complex and covalently linked to ubiquitin and rapidly degraded by proteasomes



## Molecular Mechanisms of the Development of Renal-Cell Carcinoma



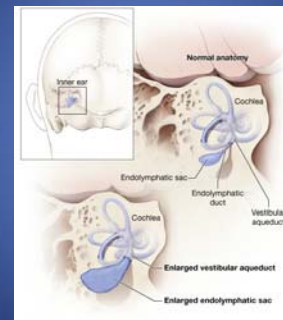
Cohen H and McGovern F. N Engl J Med 2005;353:2477-2490

THE NEW ENGLAND JOURNAL OF MEDICINE

## HIF-1: renal relevance

1. Underlies regulation of EPO
2. Parts of kidney experience low oxygen tensions, even under normal conditions, and kidney is very sensitive to hypoperfusion injury
3. Activation of HIF1 occurs in great majority of clear cell RCC. This is because VHL TSG has a critical role in regulation of HIF1. i.e. inheriting a defective VHL gene = very high risk of CCRCC and does not predispose to cancer in other organs.

## Endolymphatic Sac Anatomy

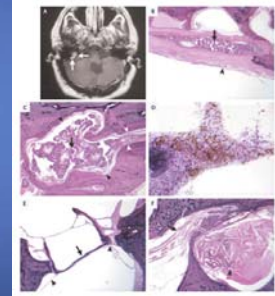


## Endolymphatic Sac Tumors

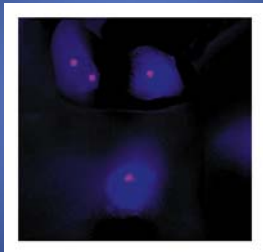
- Locally invasive neoplasms arising in the temporal bone
- Lead to morbid hearing loss, tinnitus, vertigo, aural fullness, facial nerve dysfunction
- Most often assoc VHL dz and are freq bilat
- Despite descriptions of petrous-bone lesions by Brandt and Lindau in 1920's and sporadic reports of ELS tumors in pts with VHL, not formally recognized as part of VHL dz until late 1990's.
- Bilat tumors in 30% pts with VHL who have ELS tumors

## MRI and Histologic Analysis

- A. Enhancing ELS tumor in rt temporal bone
- B. ELS tumor extends from ELD into ELS contained in post fossa dura
- C. ELS tumor is within duct and eroded contiguous region
- D. Reactive inflammatory response
- E. Distention of saccular membrane indicates EL hydrops
- F. neuronal Degeneration vestibular nerve with cholesterol clefts (reactive changes)



## FISH of cells from ELS



## Hearing Loss and Vestibular


- Pts with VHL and ELS tumors, 95% have hearing loss, 92% tinnitus, 62% have vertigo or disequilibrium, 29% aural fullness
- Hearing loss is acute and clinically significant in 43% pts and occurs over 3-6 months in another 43% pts, typically the loss is irreversible (cochlear and neuronal degeneration) and occurs early in life, mean age onset 22 y/o
- In 60% pts with VHL dz with vestibulocochlear sx's, there is no evidence on imaging of an ELS tumor, may be due to a microscopic tumor
- Hearing loss is due to invasion of tumors into inner ear vs intralabyrinthine hemorrhage, hydrops formation due to tumor

## Treatment

- Complete sx resection of ELS tumors can be curative and can be performed with preservation of hearing and alleviation of vestibular sx's
- Early intervention recommended



- [www.vhl.org](http://www.vhl.org)
  - Tissue banking
  - DNA testing
  - Research database
  - Pt and family support
  - Physician contacts



- DNA Testing for VHL
  - Anyone with 1<sup>st</sup> or 2<sup>nd</sup> deg relative with VHL is at risk
  - DNA sequencing, southern blot analysis
  - Pregnant women may request VHL as part of genetic screening

## VHLFA Research database



The VHL Family Alliance is building a research database to further the knowledge of researchers, physicians, and patients about von Hippel-Lindau disease. The VHLFA is an ideal clearing house for gathering this information. We have the largest database of VHL patients' addresses in the world. We are in a unique position to collect a vast quantity of data which will attract researchers and which, most importantly, will eventually improve diagnosis, treatment, and quality of life for people with von Hippel-Lindau disease.

## Tissue Banking

- NIH funded
- Keeps surgically removed tumor tissue on file for research
- Banking tissue, blood, urine
- Discarded surgical specimens
- Tissues and organs after death



## Annual Surveillance Protocols

- Infants and children up to age 11
  - Retinal exam including pupil dilation for r/o angiomas
  - Plasma catecholamines for pheochromocytoma
- Adolescents
  - Plasma cats and abd CT with contrast for pheochromocytoma
  - Retinal exam
  - MRI brain and spine with gad for hemangioblastoma
- Adults
  - Plasma cats and abd ct with contrasts for pheo
  - Retinal exam
  - MRI brain and entire spine with gadolinium
  - MRI or CT for RCC
  - Baseline ear, nose and throat exam including audiometry

## Survival

- A good understanding of natural history of VHL-assoc tumors had led to surveillance strategies developed for affected individuals leading to detection of small, asymptomatic tumors prior to the development of metastases, ie 'VHL family Alliance'
- Therapeutic advances: renal sparing sx in RCC

## Treatment

- Shift from radical nephrectomy to renal-sparing sx
- Contributors
  - Improved imaging with regular surveillance
  - Solid renal tumors <3cm gen low metastatic potential and are monitored
  - Partial nephrectomy appears to be as effective as total nephrectomy for early stage RCC.