Clinical Advances in the Management of VHL disease

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Disclosures-VHL Alliance meeting

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Employee of: Vanderbilt University Medical Center

I will not discuss off label use and/or investigational use in my presentation.

Outline

- Major updates to screening
- Examining the concept of the coordinator in the VHL CCCC
- Retina update
- CNS update
- Renal update
- Pheo/PGL/PNET update

VHL: By the systems

- Retinal angioma (hemangioblastoma)
- CNS hemangioblastoma
- Renal cyst/Clear cell RCC
- PHEO or paraganglioma
- ELST
- Epididymal or adnexal papillary cystadenoma
- Pancreatic cyst/pancreatic NET
Major change #1-Diagnosis

- **New (previously undetectable) disease-causing mutations in VHL**
  - Alternative exon, mutations in cryptic exon
  - Synonymous mutations with pathogenic potential
- **Diagnosis focus to identify new families based on:**
  - VHL mutation detected in 84% of apparently sporadic Hb
  - Higher than expected germline VHL in apparently sporadic pheo/PGL


Major change #2: Screening

- **Proposed changes to guidelines based screening**
- **Literature review based risk assessment for phenotypic onset** *(when should we start worrying?)*
- **Literature review based assessment of modality sensitivity and specificity for detection** *(what is the right test?)*
- **Pilot project validation of value in guideline concordant management.** *(what else does my patient have?)*

*Clin Cancer Res*, 2017 Jun 15;23(12):e68-e75

Current recommendations, screening:

<table>
<thead>
<tr>
<th></th>
<th>Pediatric (16y)</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retina</td>
<td>Annual visualization</td>
<td>Annual visualization</td>
</tr>
<tr>
<td>Brain/cerebellum (Internal auditory canal)</td>
<td>If symptomatic (if recurrent ear inf.) MRI every 2-3 years or more as needed</td>
<td>MRI every 2-3 years or more as needed</td>
</tr>
<tr>
<td>CTLS Spine</td>
<td>As above</td>
<td>As above</td>
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<tr>
<td>Audiology</td>
<td>Age 5-10, annual</td>
<td>Annual</td>
</tr>
<tr>
<td>Adrenal/Paraganglioma</td>
<td>Metanephrines-early MRI from age 16</td>
<td>Metanephrines MRI every 1-2 year</td>
</tr>
<tr>
<td>Kidney</td>
<td>Annual ultrasound (MRI if findings) Annual US or MRI, MRI at least q2y</td>
<td>Annual US or MRI, MRI at least q2y</td>
</tr>
<tr>
<td>Pancreas</td>
<td>No recommendation</td>
<td>Annual US or MRI, MRI at least q2y</td>
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</tbody>
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Emerging recommendations, screening*:

<table>
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<td>Retina</td>
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<tr>
<td>Brain/cerebellum (Internal auditory canal)</td>
<td>MRI every 2 years From age 10ish?</td>
<td>MRI every 1-3 years or more as needed</td>
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</table>
Current best strategy—stay ahead of the game

The VHL CCCC:

How well does it work, can you impact disease?

- Observational prospective clinical trial
- Define the concordance with guidelines within a CCCC vs without CCCC coordination.
- VHL natural history—how frequently do you discover “actionable” findings

- Encourage your center to partner with Dr. Anthony Daniels via the VHL Alliance

Retina clinical update
Retinal angioma-

(a) Color photograph showing a retinal capillary hemangioblastoma located at disc, (b) fundus fluorescein angiography of disc retinal capillary hemangioblastoma showing its communication with inferotemporal major vessels and absence of leakage, (c) tiny retinal capillary hemangioblastoma identified on fundus fluorescein angiography, (d) optical coherence tomography angiography of disc retinal capillary hemangioblastoma showing communication with inferotemporal major vessels


Retinal Interventions

- Laser therapy
- Radiation
- Photocoagulation
- Photodirected therapy
- Thermotherapy
- Intravitral anti-VEGF
- Propalolol*

Orphanet J Rare Dis. 2017 Jun 29;12(1):122

CNS Imaging and management

MRI imaging of cerebellar hemangioblastoma

[Images of MRI scans are shown]
MRI imaging of cerebellar hemangioblastoma-novel imaging

- Diffusion weighted
- Functional Imaging
- 3D reconstruction

*Institution and user dependent, but rapidly emerging and disseminating.

Management

- Resect symptomatic or dangerous lesions
- Restore functions lost due to tumors
- Rare use of stereotactic radiosurgery
- Advances surgical and ablative management of endolymphatic sac tumors

RCC management

US or MRI? Sensitivity and Specificity vs Feasibility and Cost
Advances in surgical or local management of RCC

- Advances in 3D imaging to enhance the surgical approach
- Increased understanding of the risks and benefits of using ablative approaches.
- Continued reliance on the 3cm rule
- Future new role for systemic therapy to prevent or delay surgery or disease spread**

Advances in systemic management of metastatic RCC

- Cabozantinib is the new first line for good risk disease
- Ipilimumab/nivolumab is the new first line for intermediate and poor risk group patients

New systemic agents are tolerated very well.

Pheo/PGL/PNET

Motzer et al NEJM 2018

Choueiri et al 2018
Pheochromocytoma/Paraganglioma

- Overall, Ga-68 DOTATATE PET/CT detected similar number but has significantly greater lesion-to-background contrast compared to F-18 FDG PET/CT.
- MRI remains the gold standard.
- MIBG scan used for identifying tumors likely to respond to MIBG therapy.


Management of PNET lesions

Monitor until 3cm (solid)

New radiopharmaceutical FDA approved options:
- advanced/metastatic disease
- Lutathera Lu-177
- Iobenguane I-131


Summary-Clinical Advances

- Advances in genetic detection will alter the commercial testing to capture a wider range of mutations.
- Changes to current guidelines will encourage earlier screening, and risk adjusted use of imaging.
- Imaging technology brings new functional and structural views to monitoring of disease.
- Emerging preventative treatments (next talk).
- New systemic therapy paradigm for metastatic renal cell carcinoma (with FDA approval)
- New radiopharmaceuticals FDA approved for treatment of PNET and Pheo/PGL.

Thank you!