VHL in Children, Adolescents, and Young Adults

VHLA Annual Family Meeting
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Outline
• History of VHL
• Two-hit hypothesis
• Function of VHL protein
• VHL manifestations in children & adolescent
• Surveillance guidelines
• Treatment/new approaches
• Genetic testing and surveillance – unique aspects in children

Disclosures
• None

History of VHL

1872: first cerebellar hemangioblastoma described
1879: retinal hemangioblastoma described
1894: von Hippel described additional case in young man
1894: von Hippel described ocular findings of 23 yo with visual loss
1904: von Hippel described ocular findings of 23 yo with visual loss, defining the syndrome
1911: neuropathologist Arvid Lindau linked ocular w/other organ findings, defining the syndrome
1927: neuropathologist Arvid Lindau linked ocular w/other organ findings, defining the syndrome
1936: Davidsohn et al coined the term “VHL disease”
1993: VHL gene sequenced by Latif et al
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1980s: chromosome 3p noted abnormal in kindreds of RCC patients
- Genetic linkage analysis further defined the position of VHL on 3p
Two-Hit Hypothesis

- 1980s: Knudson described the “two-hit hypothesis” related to oncogenic potential of tumor suppressor genes

VHL Inheritance

- Autosomal dominant (50% chance of inheriting)
- VHL is commonly passed down within families (80% inherited, 20% sporadic)
- Often know when children are young b/c of affected family member

Role of VHL Protein

- Genotype-phenotype relationships relate to how functional the VHL protein is at degrading HIF1 alpha

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Lifetime Risk of VHL-Associated Tumors

| Tumor Type | Risk | Mean Age at Diagnosis
|------------|------|----------------------|
| CNS hemangioblastoma | 50%–90% | 10–20
| Cerebellar | 5%–75% | 10–20
| Bladder | 1%–25% | 50–70
| Spinal | 1%–50% | 50–70
| Renal artery/hemangioblastoma | 25%–60% | 50–70
| Renal | 25%–75% | 50–70
| Ectopic | 1%–25% | 50–70
| RCC | 1%–50% | 50–70
| PHEO | 10%–25% | 50–70
| ELCST | 10%–15% | 50–70
| Pheochromocytoma | 35%–75% | 15–45
| Ectopic | 2% | 30–45
| NET | 10%–17% | 50–70
| Pheochromocytoma | 10% |

Redman et al. CCR 2017
VHL Manifestations in Children


- Retrospective study of 99 patients (37 Danish, 62 international)
- 70% manifested disease before age 18 years (median age 12 yr)
- Most common retinal (34%), CNS hemangioblastomas (29%)
  - Retinal: Visual outcomes significantly improved when hemangioblastomas detected before being symptomatic
  - CNS: diagnosed age 6-17 years (median age 13 yr)
- Pancreatic cysts and pheochromocytomas seen in 20% and 14%, respectively
- No broad uterine ligament involvement or ELSTs observed

VHL Manifestations in Children


- Danish cohort study, 52 patients followed for 799 patient years
- 0.4 new tumors/year. Highest risk for new tumors: age 30-34 years
- Timing of manifestations:

Natural History of CNS Hemangioblastomas

Lonser et al. J Neurosurg 2014

- Prospective natural history study (NIH) – 2001 – 2005
  - 225 patients (1921 tumors at entry) with >2 yrs follow up (median 6.9 yrs)
  - Mean age at entry: 38.5 yrs (12.3 – 66 yrs)
  - 72% had new CNS hemangioblastomas during study
  - 51% remained stable, 49% grew
  - Those age 12-20 yrs developed more tumors/yr than older counterparts (developmental/hormonal factors?)
  - 6.4% of all patients required treatment

Principles of VHL Surveillance

“Until a cure is found, surveillance is a patient’s strongest defense to prevent severe VHL complications”

- Rationale: early detection will decrease morbidity/mortality
- Duration: life-long, regardless of age
- Beyond imaging surveillance, maintain a healthy level of suspicion based on signs/symptoms
Evolution of VHL Surveillance Guidelines

<table>
<thead>
<tr>
<th>Tumor</th>
<th>VHL Alliance 2017*</th>
<th>Rednam et al. 2017* (Dominant)</th>
<th>Hoo et al. 2017* (The Netherlands)</th>
<th>Kendziera et al. 2014*</th>
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<td>RHD</td>
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<td>Annual abd imaging  &lt;5 y</td>
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<td>(alternative U.S and MRI)</td>
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<td>ELST</td>
<td>Q 4–y radiology eval &lt;5 y</td>
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<td>BI annual MRI b/h ≥ 3 y</td>
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<td>CNS HM</td>
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<td>RCC</td>
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<td>PanNET</td>
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<td>Annual abd imaging ≥ 15 y (US or MRI)</td>
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Rednam et al. CCR 2017

Current VHL Surveillance Guidelines

BP monitoring is an art
- Account for age/height
  - Sit x 5 min prior to BP

Ensure adequate retinal experience
- A few reasons for false positives...
  - Medications: antidepressants, beta blockers, sudafed, albuterol, amphetamines,
  - Foods: nuts, certain fruits
  - Other: exercise, stress

Include “thin cuts” through cerebellum & auditory canals

Other Principles:
- Reduce ionizing radiation therapy (avoid CT/Xray if possible, wear sunscreen/protective clothing)
- Avoid contact sports if adrenal or pancreatic lesion present
- Screen plasma/urine metanephrines prior to surgery or pregnancy

New Approaches

- Currently no clinical trials evaluating novel systemic therapies in children
- Targeting VHL–HIF–VEGF pathway
  - VEGF inhibitors ➔ Sunitinib, Sorafinib, Pazopanib, Axitinib, Avastin
  - mTOR inhibitors ➔ Everolimus, Temsirolimus
  - HIF2 alpha inhibitors (inhibit binding of HIF2a to DNA) ➔ in development (e.g. acriflavine)
- Gene therapy ➔ RNA interference, CRISPR?

When Do We Intervene?

- Timing depends on location, size, rate of growth
  - Retinal lesions – address right away
  - Renal and pancreatic tumors – typically >3cm
  - CNS hemangioblastomas – typically only if symptomatic or high growth rate

- In children, less is often more given near certain need for intervention in adulthood
Genetic Testing & Surveillance in Children

- Informed consent
- Timing of testing defined by patient/family
- Ongoing support to reinforce information, provide age-appropriate information and psycho-social support
- If tested when young, recommend repeat formal genetic counseling in early to late teen years & at time of family planning

Two Sides of Surveillance

- “Scanxiety” well described around the time of surveillance imaging
  - Fear of scans themselves (e.g. being in tight space)
  - Fear of findings
  - Fear of waiting between scans
- Conversely, surveillance can be empowering (knowledge = power)
  - Negative testing can provide relief
  - Surveillance team/psychology support - forms trust, someone to call

Conclusions

- VHL is commonly passed down from parent → child
- Most common manifestations in childhood: retinal/CNS hemangioblastomas, pheochromocytomas
- Surveillance guidelines are becoming more evidence-based
- Relationships between genetic counselors, medical providers, patients, and families are key

Acknowledgements

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