VHL and Neurosurgery: Side Effects of the Disease and their Therapies

von Hippel-Lindau disease

- Autosomal dominant syndrome
  - Mutation in VHL gene
    - Short arm of chromosome 3 (Laft et al., Science, 1993)
  - Incidence 1 in 39,000 births (Neumann et al., Lancet, 1987)
- Associated lesions
  - Visceral
    - Renal cell carcinoma and cysts
    - Pheochromocytomas
    - Pancreatic neuroendocrine tumors and cysts
  - Central nervous system
    - Hemangioblastomas
  - Endolymphatic sac tumors (ELSTs)

VHL Epidemiology

<table>
<thead>
<tr>
<th>VHL degree of incidence</th>
<th>1 in 36,000</th>
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<tbody>
<tr>
<td>VHL point prevalence</td>
<td>1 in 38,000</td>
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<tr>
<td>Age range of diagnosis (years)</td>
<td>Infancy to 70</td>
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<tr>
<td>Average age of diagnosis (years)</td>
<td>26-29</td>
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<td>Average age for full penetrance of VHL</td>
<td>70</td>
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<tr>
<td>Male-female penetrance</td>
<td>1:1</td>
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<tr>
<td>De novo VHL mutations</td>
<td>20%</td>
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<tr>
<td>Familial VHL mutations</td>
<td>80%</td>
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CNS Manifestations

- Hemangioblastomas
  - Cerebellar
  - Brain stem
  - Spinal cord
  - Spinal nerve roots

- Endolymphatic Sac Tumors (ELST)

Hemangioblastoma

- WHO Grade I Tumor (benign)
- Vacuolated cells with hyperchromatic nuclei surrounded by a rich capillary network

2884 Hemangioblastomas

- Supratentorial (27 tumors; 1%)
- Brainstem (153 tumors; 6%)
- Cerebellum (1335 tumors; 48%)
- Spinal cord (1581 tumors; 36%)
- Cauda equina (361 tumors; 10%)

von Hippel-Lindau Disease-Associated Hemangioblastomas Are Derived from Embryologic Multipotent Cells
Embryonic Hemangioma and Hemangioblastoma cells produce 3 protein markers:

- Brachyury
- Fik-1 (VEGF receptor-2)
- SCL (stem cell leukemia)

Neuro-anatomic Location

- Posterior Fossa (Infratentorial)
  - Cerebellum
    - Posterior > Anterior
  - Brainstem
    - Posterior medulla > Elsewhere in brainstem
- Supratentorial

<table>
<thead>
<tr>
<th>Location</th>
<th>Signs and symptoms (%)**</th>
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<tbody>
<tr>
<td>Cerebellum</td>
<td>Headaches (76%), gait ataxia (64%), dysmetria (64%), diplopia (8%), vertigo (8%), emesis (8%)</td>
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<tr>
<td>Brainstem</td>
<td>Hypesthesia (55%), gait ataxia (22%), dysphagia (22%), hyperreflexia (22%), headaches (11%), dysmetria (11%)</td>
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<tr>
<td>Spinal cord</td>
<td>Hypesthesia (83%), weakness (65%), gait ataxia (65%), hyperreflexia (52%), pain (17%), incontinence (14%)</td>
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</table>

**Mean age at symptom formation 33±10 years
In Cerebellum: 82% in the hemisphere
18% in the vermis

So, why is it a problem in the brain?

- Limited space
  - Tumor growth
  - Swelling
  - Cyst
In Brainstem: 71% in the obex
Signs and Symptoms of HB’s are due to:
- Tumor Growth and/or
- Development of peri-tumoral cysts
  - Peri-tumoral cysts are associated with:
    - 72% of symptomatic cerebellar tumors
    - 75% of symptomatic brainstem tumors
    - 95% of symptomatic spinal cord tumors
  - Rate of cyst enlargement compared to the tumor
    - 7 times faster in cerebellum
    - 15 times faster in brainstem
  - Cyst size compared to the solid tumor
    - 34 times larger in cerebellum
    - 19 times larger in brainstem

Growth
- In a review of 143 Hemangioblastomas followed for a mean of 12 years, 138/143 (97%) of tumors demonstrated radiographic growth
  - 134 (94%) tumors displayed a stuttering (saltatory) growth
  - 4 (6%) displayed progressive growth

Role of radiation therapy (?)

Radiotherapy
- 186 Pts with 517 lesion.
- Overall survival rates of 94% at 3 years, 90% at 5 years, and 74% at 10 years.
- Associated tumor control rates were 92% at 3 years, 89% at 5 years, and 79% at 10 years.

Kano et al J Neurosurg 2015
In Summary:

- Median age of CNS hemangioblastoma diagnosis = 20-30s
- Age of onset Male = Female
- Lesions primarily occur in the cerebellum, brainstem and spinal cord
- Most are asymptomatic
- Most commonly become symptomatic with cyst formation
- Symptoms due to tumor/cyst size and location
- Non-cystic tumors may develop cysts

In Summary (cont.)

- Stuttering growth (94%) > progressive growth (6%)
- Lesions do not progress in a time ordered fashion
- Spontaneous regression not common
- Treatment indicated only when symptomatic
- Surgery generally the primary treatment of choice with a very low recurrence rate
- Use of fractionated and stereotactic radiosurgery effective in selected cases but remains controversial

Thank You