Endocrinological Advances in the Management of VHL

VHL
The Moffitt Cancer Center Experience

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Endocrine Manifestations of VHL

- Neuroendocrine tumors
- Pheochromocytoma
- Paraganglioma

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VHL Endocrine Tumors

- Pancreatic neuroendocrine lesions
  - Ductuloinuslar complexes
  - Islet dysplasia
  - Microadenomas
  - Neuroendocrine tumors

Pheochromocytomas and Extra-Adrenal paragangliomas

- Characteristic of VHL although not specific

A thick vascular tumor capsule is a distinctive feature of VHL-related pheos and paragangliomas.

well-demarcated, variegated, and red-brown to yellow tan masses, most commonly in the background of cystic disease.

Pancreatic cysts

- A Pheochromocytoma is a tumor arising from adrenal medullary chromaffin cells that commonly produces one or more catecholamines:
  - Epinephrine
  - Norepinephrine
  - Dopamine
  - Rarely, these tumors are biochemically silent

- A paraganglioma is a tumor derived from extra adrenal chromaffin cells of the sympathetic paravertebral ganglia of
  - Thorax
  - Abdomen
  - Pelvis

- 80 to 85% of chromaffin-cell tumors are pheochromocytomas, whereas 15 to 20% are paragangliomas

- Evidence demonstrates that hereditary pheochromocytomas/paragangliomas (PPGLs) are characterized by:
  - distinct clinical presentations
  - Differences in biological behavior
  - Mode of transmission that reflects underlying mutations

VHL Alliance, 2017
Tampa, FL
Biochemical and radiologic Evaluation for a Pheochromocytoma/Paraganglioma

- We recommend that initial biochemical testing for PPGLs should include measurements of plasma free metanephrines or urinary fractionated metanephrines.
- We also recommend an MRI of the abdomen/pelvis for screening.
**VHL Pheochromocytomas**

- Frequently bilateral
- Paragangliomas are common
  - Mediastinum
  - Abdominal
  - Pelvic
- Type II VHL only
- Genotype-Phenotype correlations are documented and specific mutations are associated with particular patterns of tumor formation
- 98 percent of cases: the pheochromocytoma is associated with missense mutations in the VHL gene (rather than truncating or null mutations)

**Phenotype of MEN2 verses VHL syndrome: Pheochromocytoma characteristics**

- MEN-2 are more symptomatic than VHL patients
- MEN-2 have a higher incidence of hypertension (primarily paroxysmal)
- MEN-2 have higher concentrations of metanephrine (epinephrine metabolite)
- VHL have elevated serum normetanephrine (norepinephrine metabolite)
- VHL have lower total tissue contents of catecholamines and expression of tyrosine hydroxylase (the rate-limiting enzyme in catecholamine synthesis)
- VHL has a much lower expression of phenylethanolamine N-methyltransferase (PNMT) which converts norepinephrine to epinephrine. Results in lower epinephrine tissue stores.

**Preparation for surgery**

- All patients with a hormonally functional PPGL should undergo preoperative blockade to prevent perioperative cardiovascular complications.
- Adrenergic receptor blockers are the first choice.
- High-sodium diet reverses blood volume contraction, prevents orthostatic hypotension before surgery, and reduces the risk of significant hypotension after surgery.
- Preoperative co-administration of adrenergic receptor blockers should be considered.
  - To control tachycardia
  - Only after adrenergic receptor blockers have been adequately adjusted.

**VHL Endocrine Tumors**

**Type 2 VHL**
- Pheochromocytomas only occur in Type II VHL
- Associated with missense mutations

**Type 1 VHL**
- Type I VHL is usually caused by whole or partial gene deletion or a nonsense mutation
VHL Program at the Moffitt Cancer Center

In Summary

- At the first visit our VHL patients are evaluated with laboratory studies to include a Plasma and 24 hour urine fractionated metanephrine levels
- MRI for the initial evaluation and then screening exams
- Prompt evaluation with further radiologic studies are considered
- Surgical consultation when a tumor is detected
- Pre-surgical preparation with alpha blockade and close hemodynamic monitoring
- And most importantly:

Total care of our VHL patients in a supportive well coordinated manner