VHL and the Endocrine System

Cary N. Mariash, MD
Professor of Clinical Medicine, IU School of Medicine
Division of Endocrinology

19 October 2019
Presentation Outline

• What is endocrinology
• Why VHL and endocrinology
• Types of endocrine problems
  • Common problem
  • Rarer problems
• Testing for endocrine issues
• Expected follow-up with endocrinology
What is Endocrinology

• “ology” means the study of
• “endocrine” means secreting internally, i.e., hormones
• Study of the glands that secrete hormones, and the function of those hormones
• Examples

<table>
<thead>
<tr>
<th>Gland</th>
<th>Hormone</th>
<th>Disease(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid</td>
<td>Thyroid hormone</td>
<td>Hyperthyroidism (overactive thyroid, Graves’ Disease)</td>
</tr>
<tr>
<td></td>
<td>(thyroxine)</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>Insulin</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>Adrenal Cortex</td>
<td>Cortisone</td>
<td>Addison’s Disease (too little), Cushing’s Disease (too much)</td>
</tr>
<tr>
<td>Adrenal Medulla</td>
<td>Adrenaline, Noradrenaline</td>
<td>Pheochromocytoma (too much)</td>
</tr>
<tr>
<td>Ovaries, Testes</td>
<td>Estrogen, Testosterone</td>
<td>Infertility</td>
</tr>
</tbody>
</table>
Pituitary gland ("Master Gland")
What is VHL

• Von Hippel-Lindau disease is due to a genetic mutation of the VHL gene leading to an altered VHL protein
• The VHL gene is a “tumor suppressor gene”
• When there is a mutation in the protein, tumors can develop in tissues that express the VHL gene
• Many of these tissues are part of the neuro-endocrine system
  • Adrenal Medulla - pheochromocytoma
  • Other nerve tissue (Sympathetic nervous system) - paraganglioma
  • Endocrine pancreas – pancreatic neuro-endocrine tumor
Adrenal Medulla -- Fight or Flight Response

• Adrenal Medulla hormones are controlled by the nervous system
  • When stress or fear is sensed, brain sends signal down sympathetic nervous system to adrenal medulla
  • Signal causes the adrenal medulla to release epinephrine (adrenaline) and norepinephrine (noradrenaline) to the rest of the body

• Epinephrine
  • Stimulates heart rate to increase so more blood can go to muscles
  • Allows liver to release sugar to raise blood sugar
  • Increases sweating

• Norepinephrine
  • Works with epinephrine
  • Constricts blood vessels to raise the blood pressure
Pheochromocytoma (1)

• Tumor of adrenal medulla is called pheochromocytoma
• Epinephrine and norepinephrine no longer under normal control from the brain
  • Rapid heart rate can occur for no particular reason
  • Blood pressure can zoom way up and remain up
    • Stroke
    • Heart attack
• Any time the pheochromocytoma is touched can lead to hormone release
• Pheochromocytoma can be in one or both adrenals
Pheochromocytoma (2)

• Epinephrine is metabolized to metanephrine
• Norepinephrine is metabolized to normetanephrine
• Metabolism products are not active but stay around in the system
• Test for pheochromocytoma by measuring:
  • Blood metanephrine and normetanephrine, or
  • 24 hour urine levels of metanephrine and normetanephrines
  • May also measure urine epinephrine, norepinephrine, and dopamine
• If blood or urine test is positive, then MRI or CT of abdomen is next step to see where the tumor is located
Pheochromocytoma (3)

- Treatment is surgical removal of tumor
- Patient is prepared for surgery by giving drugs that block the effect of epinephrine and norepinephrine
  - Alpha blockers given until blood pressure is good
    - Prazosin, terazosin, doxazosin, or phenoxybenzamine
    - Then beta blocker is added (propranolol and others)
- Usually takes at least 2 weeks of drug preparation prior to safe surgery
Pheochromocytoma (4)

- In VHL patients, screening for disease should start at age 5
- Screening should continue yearly for life
- About 25% of VHL patients will have a pheochromocytoma
- Many of these are in both adrenals, but the occurrence in the second adrenal can occur at any time
- Paragangliomas look like pheochromocytomas under the microscope, but usually do not secrete excess epinephrine and norepinephrine (but they may)
Other Endocrine Disease in VHL

- Pancreatic neuro-endocrine tumors (PNET) are common
  - Frequently contain one or more hormones such as insulin, glucagon, gastrin
  - Excess secretion of these hormones are uncommon
- If large amounts of pancreas are removed to treat PNET, then insulin deficiency may occur leading to diabetes mellitus
- If both adrenal glands removed for bilateral pheochromocytoma, then deficiency of cortisol is also present and requires lifelong treatment
Summary

• Endocrinology is the study of hormones secreted by glands which includes adrenaline which comes from adrenal glands

• VHL leads to endocrine disease in about 25% of patients due to development of a pheochromocytoma

• Screening for pheochromocytoma starts at age 5 and is done by blood or urine testing

• Pancreatic neuro-endocrine tumors occur in about 10% of VHL patients and usually do not secrete excess hormones (but may)