UNIVERSITY OF MICHIGAN

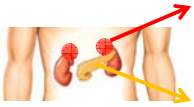
VHL AND THE ADRENAL GLAND & PANCREAS

Tobias Else, MD
MEND, Metabolism, Endocrinology and Diabetes
Internal Medicine, University of Michigan Health System

Adrenal and pancreatic tumors & VHL

- Introduction to organ function & physiology
  - Adrenal glands
  - Pancreas
- Diagnosis – Surveillance – Therapy
- Summary

Organ function: Adrenal & Pancreas



Stress response, blood pressure, salt balance etc.
→ Absence of adrenal glands → Adrenal insufficiency
Therapy: hormone replacement

Blood glucose levels, provides enzymes for digestion
→ Absence of pancreas → Maldigestion
→ Diabetes
Therapy: Insulin & oral enzyme replacement

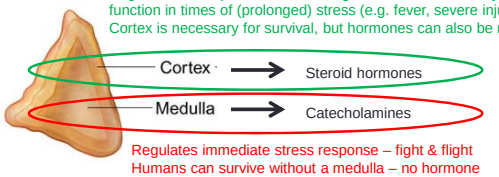
→ **Adrenal glands & pancreas are necessary to survive, but absence of organ (e.g. after surgery) can be treated medically.**

→ **Best to avoid complete absence of function because of reduction in quality of life & complications resulting from reduced function & therapy**

The adrenal – two organs in one

- Adrenal anatomy & function

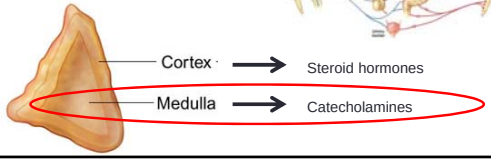
Regulates blood pressure, blood sugar and maintains body function in times of (prolonged) stress (e.g. fever, severe injury)
Cortex is necessary for survival, but hormones can also be replaced



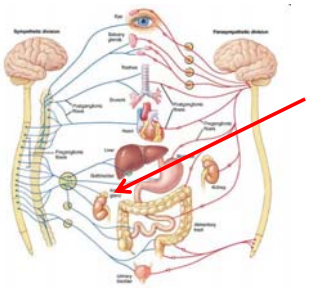
Regulates immediate stress response – fight & flight
Humans can survive without a medulla – no hormone replacement necessary

Pheochromocytoma

- Are tumors of the adrenal medulla (or autonomous nervous system)
- Produce catecholamines (=adrenaline, noradrenaline)
- Can lead to episodic symptoms of
  - Racing heart beat
  - Headaches
  - Pallor
  - Sweating
  - High blood pressure



The autonomous nervous system



Adrenal gland – pheochromocytoma

Everywhere else – paraganglioma

Pheochromocytoma & VHL

Pheochromocytoma
- occur in some VHL families ('genotype – phenotype – correlation')
- ~20% of VHL patients will have a pheochromocytoma
- Tumors can be bilateral
- Tumors are almost always (96%) benign – not cancer
- Can be the only manifestation of VHL
- Can occur in children, adolescents and adults

- Diagnosis is made by
  - Elevated products of noradrenaline (normetanephrine) in blood or serum → normetanephrine levels are almost always elevated in VHL-associated pheochromocytoma
  - Imaging, preferable MRI or CT, occasional MIBG or FDG-PET scan

→ Symptoms & level of normetanephrine depend on size!
→ Most pheochromocytoma in VHL found during surveillance do NOT cause symptoms

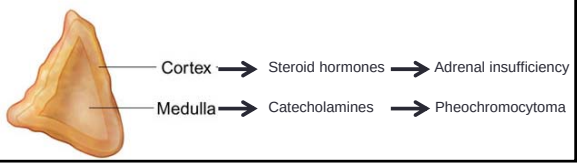
Surveillance of patients at risk

- Physical exam
  - Blood pressure?
- History
  - Episodes of pallor, sweating, high blood pressure?
- Blood draw
  - Elevated normetanephrine levels?
- Imaging
  - Adrenal tumors?

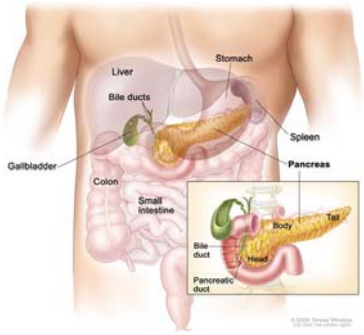
- Start screening at least at age 10 - annually
- Screening will catch most pheochromocytomas early

Therapy

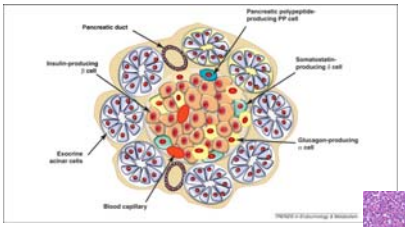
- Surgery
  - Touching the tumor during surgery can lead to release of noradrenaline → increase blood pressure!
  - Blood pressure control prior to surgery with
    - Alpha blockers (and beta blockers)
    - Calcium antagonists
  - Most experienced surgeons will try to do cortex-sparing surgery

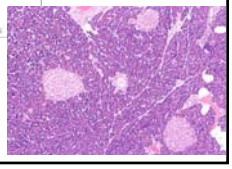


The pancreas

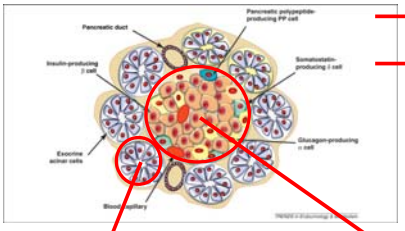


The pancreas – two organs in one





Tumors of the pancreas & VHL



Cystadenoma

Pancreatic cysts

VHL - associated

Pancreatic cancer
(adenocarcinoma, malignant)
→ **No increased risk with VHL**

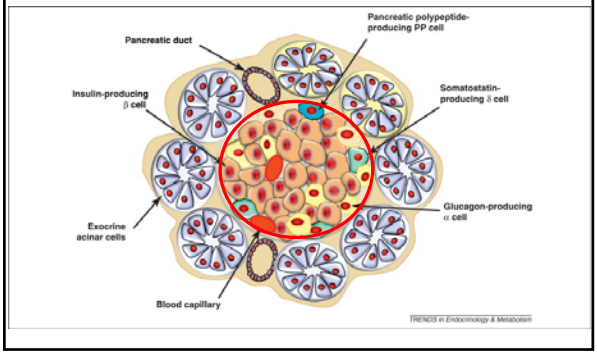
Neuroendocrine tumors

Tumors of the pancreas

- Pancreatic cysts
  - Commonly found in VHL patients
  - Often 'incidental' finding
  - No treatment unless compressing other structures or symptoms (e.g. pain)
- Serous cystadenoma
  - Commonly found in VHL patients
  - Often 'incidental' finding
  - No treatment unless compressing other structures or symptoms (e.g. pain)

→ Neither lesion will progress to cancer !
→ Usually NO therapy

Neuroendocrine tumors (NETs) of the pancreas



NETs & VHL

Facts
- 10-20% of VHL patients will have a pancreatic NET
- Only ~10% of NETs are obviously malignant
  → Higher risk for tumor > 3cm, exon 3 mutation, fast growth
- VHL-associated NETs do not produce hormones
  → Rarely symptoms
- Diagnosis in 30s – 40s (youngest described ~12yrs)

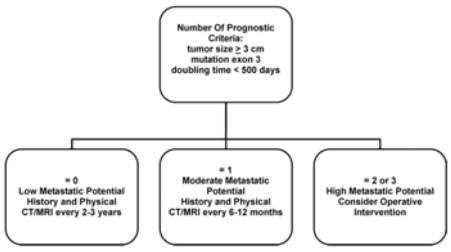
Diagnosis
- Imaging
  - Screening MRI (~every 6 month – 3 years)
    - Visualization during surveillance for RCC
  - Dedicated CT scan or octreotide scan to evaluate extent
  - Endoscopic ultrasound
- Laboratory evaluation
  - Chromogranin A, pancreatic polypeptide, others

Initial therapy

- Surgery
  - Surgery, Surgery, Surgery …
  - … but at the right time!
  - As little as possible and as much as necessary!
- Recommendation for surgery
  - NETs > 3 cm (between 2-3) surgery may be considered
  - Fast growing tumors
  - Patients with exon 3 mutations
- Extent of surgery depends on location of tumor in the pancreas
- Intraoperative palpation and ultrasound may help to identify additional NETs
- However, in order to preserve pancreatic function, small tumors can be left in place and followed

  → Prevent Diabetes due to complete pancreatectomy!

Flowchart for NET decision making



- Caution with tumors 2-3 cm – individualize therapy & surveillance!

Blansfield et al., Surgery 2007

Therapy for advanced NETs

- Surgery
  - Surgery, Surgery, Surgery …
    - 'Debulking' = decreasing tumor load
  - Local therapies
    - Chemoembolization
    - Radiofrequency ablation
- Medical therapy
  - Octreotide
  - mTOR inhibitors
    - **everolimus**
  - Tyrosine kinase inhibitors
    - **sunitinib**
  - Chemotherapy
    - Streptozotocin/5FU
  - Peptide receptor therapy

Summary

- General surveillance
  - Guidelines – see VHLFA handbook !
- Diagnosis surveillance and therapy should be individualized
  - Every patient is different
- Neuroendocrine tumors and pheochromocytomas start as 'benign' lesions
- Surgery
  - Right time
  - Right extent
  - Organ & organ function preserving

  → prevent adrenal insufficiency and diabetes
- Medical treatment for the rare metastasized NETs is improving

UNIVERSITY OF MICHIGAN

Thank you for your attention!

Tobias Else, MD
Endocrine Oncology Clinic & Cancer Genetics Clinic
MEND, Metabolism, Endocrinology and Diabetes
Internal Medicine, University of Michigan Health System
telse@umich.edu