Pheochromocytoma:
Advances in diagnosis and treatment

VHL Family Alliance
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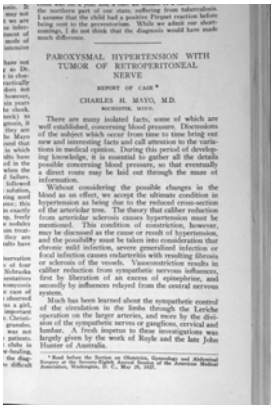
18 yo woman with intermittent attacks of palpitations, anxiety, vertigo, headache, vomiting, and constipation. Pulse rapid and strong.

Bouts of fever, dyspnea, chest pain, and cold sweats. Vision deteriorated.

Died after 9 days of inpatient treatment. Autopsy revealed bilateral adrenal tumors that stained brown when treated with chromium salts.

Early Investigations

- Felix Frankel's case report in 1886
- Terms "paraganglioma" and "pheochromocytoma" coined in early 1900s
- Marcel Labbé correlates paroxysmal hypertension to pathological finding of pheochromocytomas in 1922
- Successful surgical treatment of pheochromocytoma in 1926 by César Roux and Charles Mayo



PAROXYSMAL HYPERTENSION WITH TUMOR OF RETROPERITONEAL NERVE

REPORT OF CASE*

CHARLES H. MAYO, M.D.

ROCHESTER, MINN.

There are many isolated facts, some of which are well established, concerning blood pressure. Discussions of the subject which occur from time to time bring out new and interesting facts and call attention to the variations in medical opinion. During this period of developing knowledge, it is essential to gather all the details possible concerning blood pressure, so that eventually a direct route may be laid out through the maze of information.

Without considering the possible changes in the blood as an effect, we accept the ultimate condition in hypertension as being due to the reduced cross-section of the arterial tree. The theory that caliber reduction from arteriolar sclerosis causes hypertension must be mentioned. This condition of constriction, however, may be discussed as the cause or result of hypertension, and the possibility must be taken into consideration that chronic mild infection, severe generalized infection or focal infection causes endarteritis with resulting fibrosis or sclerosis of the vessels. Vasoconstriction results in caliber reduction from sympathetic nervous influences, first by liberation of an excess of epinephrine, and secondly by influences relayed from the central nervous system.

Much has been learned about the sympathetic control of the circulation in the limbs through the Leriche operation on the larger arteries, and more by the division of the sympathetic nerves or ganglions, cervical and lumbar. A fresh impetus to these investigations was largely given by the work of Royle and the late John Hunter of Australia.

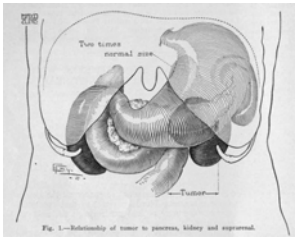


Fig. 1.—Relationship of tumor to pancreas, kidney and suprarenal.

Mayo, JAMA 1927

Surgical complications

- Initial perioperative mortality rate 50%
- By 1951, mortality rate declined to 26%
- By 2001, mortality rate declined to 2.3%

Plouin, JCEM 2001

Duh, JCEM 2001

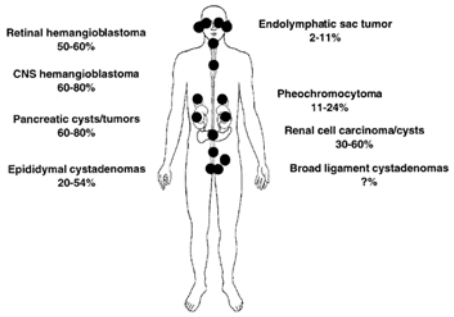
Morbidity and mortality from pheo

- Catecholamine-secreting tumors
- Rapid, potent effect on blood pressure and heart rate
- Consequences include stroke, heart attack and other heart diseases, shock, kidney failure, death
- Complications of untreated pheo, surgical complications, post-surgical complications
- "Biological time bomb"

Pheochromocytoma: Recent developments

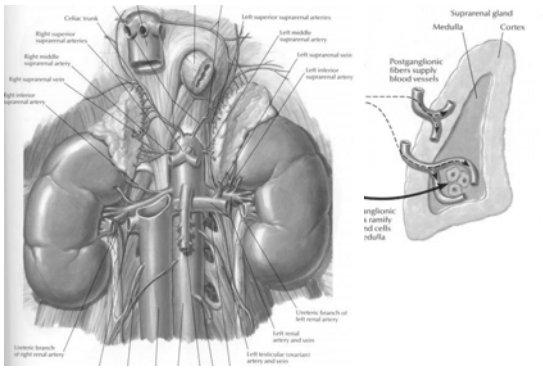
- Diagnostic tests
- Underlying genetics
- Advances in therapy
- Debunking old axioms: “The 10% tumor”
  - 10% bilateral
  - 10% malignant
  - 10% in children
  - 10% extra-adrenal
  - 10% familial

Clinical manifestations of VHL



Richard, Neurosurg Rev 2000

Adrenal glands



Pheochromocytoma in VHL

TABLE 1. Classification of VHL disease[1]

Lesions	Type 1	Type 2A	Type 2B	Type 2C
Pheochromocytoma	Absent	Present	Present	Present
Renal cell carcinoma	Present	Absent	Present	Absent
Pancreatic tumor	Present	Absent	Present	Absent
CNS hemangioblastoma	Present	Present	Present	Absent
Retinal hemangioblastoma	Present	Present	Present	Absent
Endolymphatic sac tumor	Present	Present	Present	Absent
Frequent alterations	Mutations (686T to C) Deletions Insertions	Mutations (505T to C)	Mutations (712C to T)	Mutations

[1]Based on Neumann et al. (1995) and Richard et al. (2000).

- Likelihood of pheo low but not zero in Type 1 VHL
- Likelihood of pheo ~90% in Type 2 VHL

Pathogenesis of VHL

VHL/Elongin complex + 0_2

\- (Degrades)

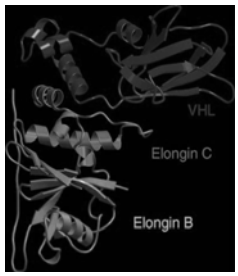
HIF-1, HIF-2

\+

Growth factors:
VEGF, TGF-α, PDGF-β

\+

Promotion of angiogenesis
Inhibition of apoptosis



Pheochromocytoma in VHL vs sporadic

- Earlier onset in VHL (mean age 30 years)
- Pediatric cases more frequent
- Up to 20% extra-adrenal
- 35% of pts are asymptomatic
- Up to 50% of cases involve both adrenal glands

Clinical evaluation: Old and new

- Classic triad: Headache, diaphoresis, palpitations
- Episodic symptoms or "spells"
- Episodic hypertension
- "Think of it!"

- Surveillance in patients known to harbor familial syndromes
- Annual catecholamine measurements for VHL, consider imaging

Stein, Medicine 1991

How to think about screening tests: Part 1

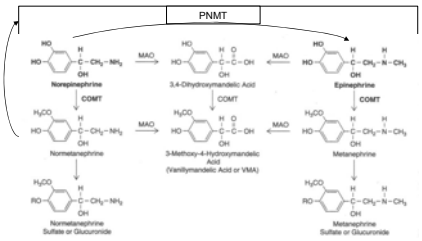
- Sensitivity
  - A sensitive test is always positive when the disease is present
  - Example, the trigger-happy fire alarm
  - Alarm silent?
  - Alarm ringing?

How to think about screening tests: Part 2

- Specificity
  - A specific test is always negative when the disease is absent
  - Example, fire alarm with higher threshold
  - Alarm silent?
  - Alarm ringing?

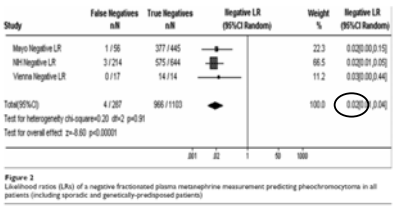
Screening tests: Catecholamine-based

- 24 hour urine collection for catecholamines, metanephrines, and VMA ($139)
- Plasma free metanephrines ($68)
- Pheos secrete AND metabolize catecholamines



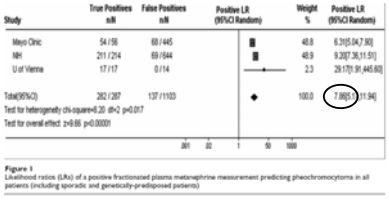
Plasma free metanephrines

- Introduced in 2002 by NIH group
- Initially reported sens 99%, spec 89%
- Follow up studies: sens 96%, spec 85%
- Technique: IV placed, pt supine for >20 min, HPLC
- Acetaminophen interferes with assay



Lenders, JAMA 2002; Sawka, BMC Endo Disord 2004

Plasma free metanephrines



- PFM highly sensitive
- Performs better in high-risk populations
- Single negative test effectively excludes pheo
- Relatively low specificity

Lenders, JAMA 2002; Sawka, BMC Endo Disord 2004

24 hr urine testing

- Test characteristics depend on cutoff values
- Beyond the 95% reference range
- What to expect in hypertensive pts

	95% ref	Suggested cutoff
Total metanephrines	3.6 µmol/day	6.6 µmol/day
Normetanephrine		
Metanephrine		
Norepinephrine	473 nmol/day	1005 nmol/day
Epinephrine	109 nmol/day	191 nmol/day
Dopamine	2612 nmol/day	4571 nmol/day
VMA		40 µmol/day

Kudva, JCEM 2003

Interpretation of catecholamine-based tests

Test	Definitions	Sens	Spec
Plasma free metanephrine	Paired test, positive if either or both values elevated	99%	89%
Plasma free normetanephrine			
Urinary epinephrine		29%	99.6%
Urinary norepinephrine		50%	99.6%
Urinary total metanephrines		71%	99.6%
Urinary total metanephrines ***and*** fractionated catecholamines	Grouped test, positive if any one of following three urinary values elevated: total metanephrines, epinephrine, norepinephrine	88%	99%
Urinary VMA		64%	95%
Clonidine suppression test			
Plasma free normetanephrine	Positive result = elevated level after clonidine ***and*** fall of less than 40%	96%	100%

Confounding factors

Medication or condition	Test(s) confounded
Tricyclic antidepressants	Urinary catecholamines and metanephrines, plasma free metanephrines
Clozapine	Urinary catecholamines and metanephrines
Phenoxybenzamine	Plasma free metanephrines
Calcium channel blockers	Plasma norepinephrine, urinary norepinephrine, urinary epinephrine
β-adrenergic blockers	Urinary catecholamines and metanephrines, plasma free metanephrines (minor effect)
α_1-adrenergic blockers	Urinary norepinephrine
Sympathomimetics	Urinary catecholamines and metanephrines, plasma free metanephrines
Buspirone	Urinary metanephrines
Major physical or psychological stress (hypoglycemia, hypoxia, hypovolemia, stroke, surgery, myocardial infarction, heart failure, severe pain, depression, panic disorder, sleep apnea)	Urinary catecholamines and metanephrines, plasma free metanephrines

Harding & Yeh, Med J Aust 2005

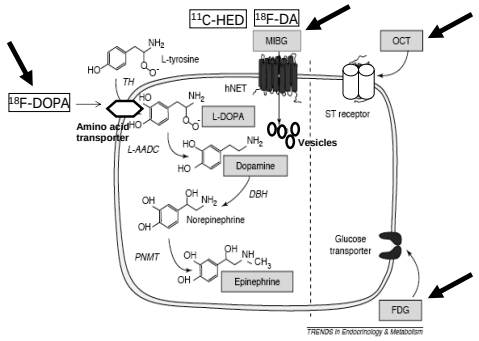
Next step in evaluation

- Positive catecholamine test should prompt either confirmatory testing or imaging
- Anatomic imaging: CT, MRI
- Functional imaging: MIBG, FDG-PET, FDOPA PET
- Co-registered imaging: FDG-PET/CT, FDOPA-PET/CT

Imaging options: Strengths and weaknesses

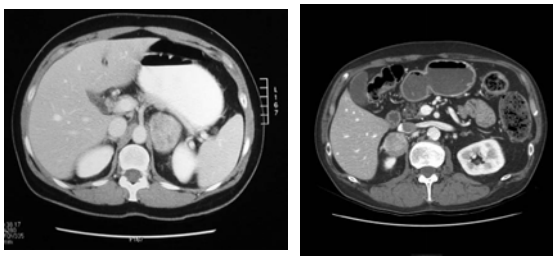
- CT: sens >90%, spec 50%
- MRI: sens >90%, spec 50%
- MIBG: sens 77-90%, spec 95%
- FDOPA-PET and FDOPA-PET/CT
  - Hoegerle 2002: sens 100%, spec 100%
  - UCLA experience (Imani/Yeh 2009): sens approaches 100%, spec 100%
- Limitations of FDOPA scanning

Pheo cell-specific targets for functional imaging

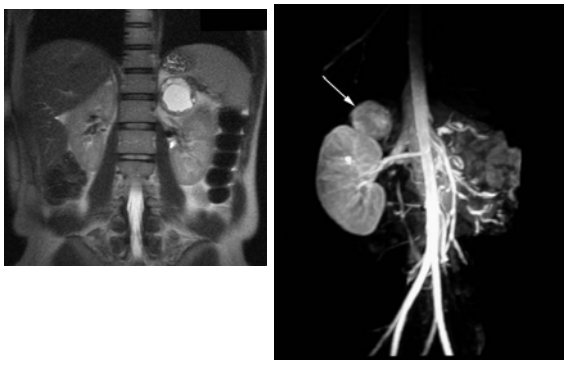


Ilias, Trends Endocrinol. Metab 2005

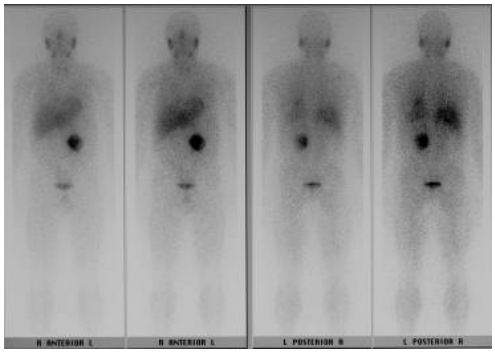
CT



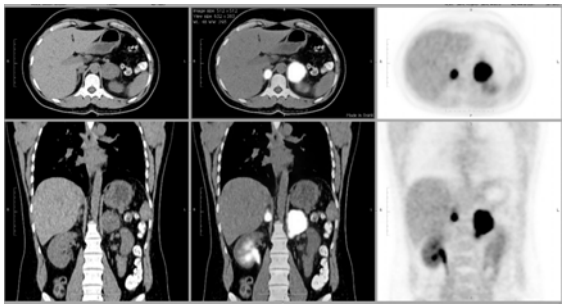
MRI



MIBG



FDOPA-PET CT



How commonly is pheo familial?

Author	# pheos	Germline mutation found	Citation
Neumann *et al.*	271	66 (24%)	NEJM/2002
Bauters *et al.*	21	7 (33%)	J Med Genet/2003
Astuti *et al.*	14	3 (21%) SDH mutations only	Clin Endo/2003

- Known: RET, VHL, NF-1
- New: **SDHB, SDHD** – common, highly penetrant
- Family screening recommended for all pheo cases <50 yo

Benn, JCEM 2006

SDHB/SDHD Familial Syndromes

• Mechanism: HIF-1α vs. somatic loss of maternal 11p15

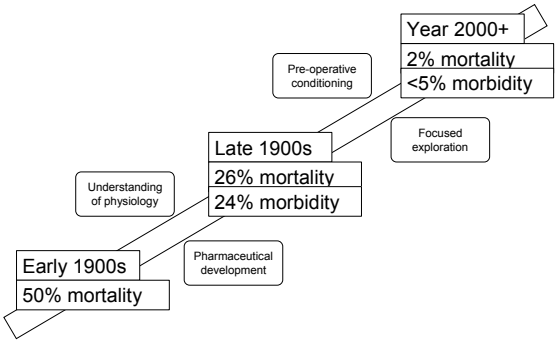
SDHB MUTATIONS
- Extra-adrenal pheos (abdominal or thoracic)
- 30-50% malignancy

SDHD MUTATIONS
- Head and neck paragangliomas
- Multiple tumors
- Earlier age of onset

Neumann, JAMA 2004

Benn, JCEM 2006

Pheochromocytoma: Advances in surgical treatment



Preoperative conditioning

• Phenoxybenzamine 10 mg BID, titrate to orthostatic hypotension and nasal congestion

• α1-selective agents: prazosin, doxazosin

• β-blockers?

• Volume expansion?

Laparoscopic adrenalectomy

• Surgery for pheo is curative in >90% of cases

• 85% of cases can be accomplished laparoscopically

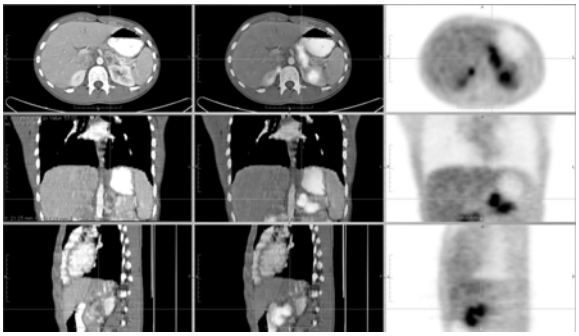
• No firm upper size limit (soft limit 6 cm)

• Open resection if suspected to be malignant preoperatively

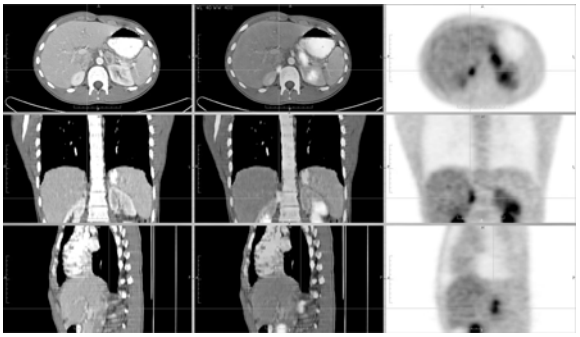
Case 1

- 15 yo boy with retinal angioma
- Positive for VHL (de novo mutation)
- Blood and urine catecholamines positive

Case 1: VHL



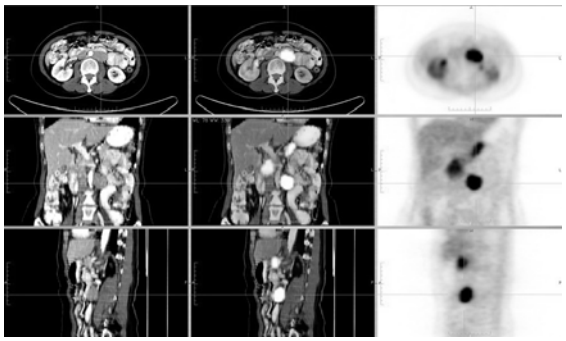
Case 1: VHL

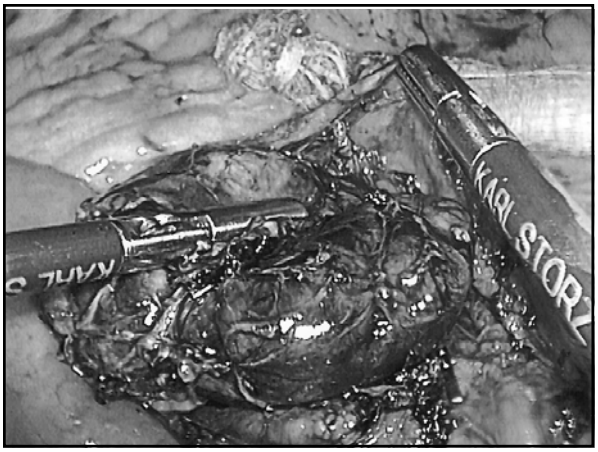


Case 2: VHL

- 49 yo woman with multiple hemangiomas of the liver, head, uterus, ovary. Multiple relatives with hemangiomas.
- Left peri-aortic mass found on CT
- Blood and urine catecholamines positive

Case 2: VHL

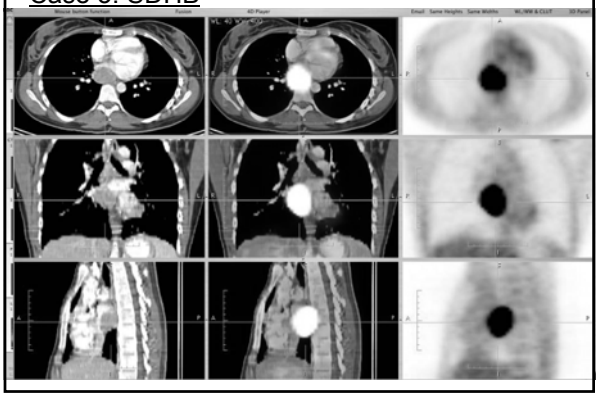


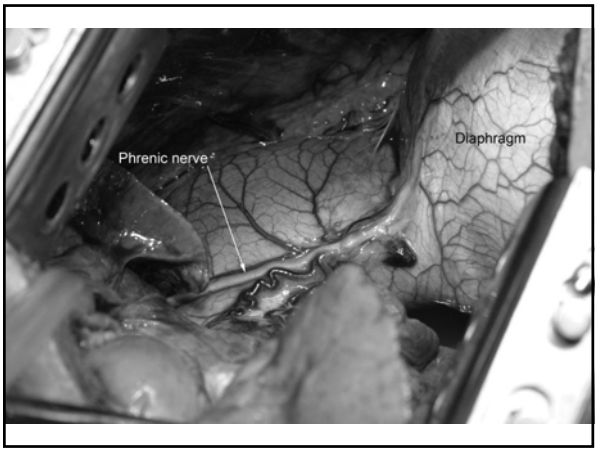


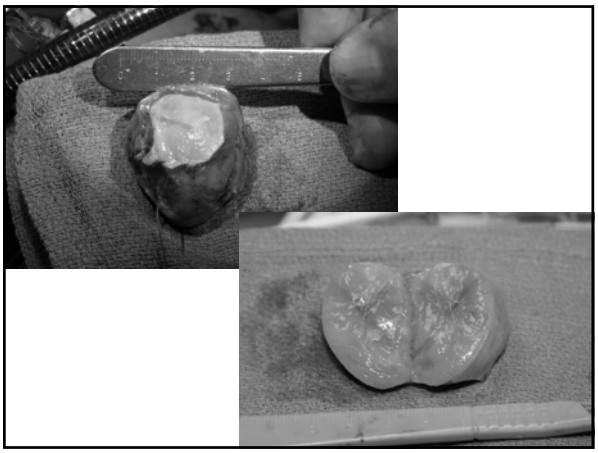
Case 3: SDHB

- 24 yo pregnant woman with hypertension
- Blood and urine catecholamines positive
- Undergoes failed surgery elsewhere
- Personal and family history suggestive of an inherited syndrome

Case 3: SDHB

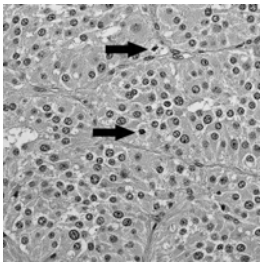


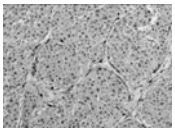




Final diagnosis

- Cardiac paraganglioma
- Familial pheochromocytoma/paraganglioma syndrome
- SDHB mutation





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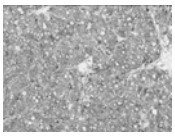

Synapto
-physin

Summary

- Pheos are common in Type 2 VHL
- Annual catecholamine-based screening is a must
- Novel co-registered imaging tests are available (sort of)
- Multidisciplinary team approach yields optimal care of these patients with rare and high risk conditions
- Compatible with long and healthy life!