

## Presentation, Diagnosis and Medical Management of Pheochromocytoma

Ronald M. Lechan, M.D., Ph.D.  
Professor of Medicine  
Chief, Division of Endocrinology  
Tufts-New England Medical Center

## Diagnosis and Medical Management of Pheochromocytoma

- **STEP I:** Clinical Suspicion
- **STEP II:** Biochemical Diagnosis
- **STEP III:** Localization of the Tumor
- **STEP IV:** Pharmacologic Treatment

## Pheochromocytoma: Clinical Presentation

- **Hypertension (80%)**
  - Sustained in 50%; paroxysmal 30%; 20% normotensive
  - Due to release of NE and E; other vasoactive substances may contribute
  - Poor correlation between BP and catecholamines
    - Variation in secretion rate, degradation, receptor number, sensitivity, co-secretion of substances than can affect vascular responsiveness (VIP, adrenomedullin, CGRP, NPY, methionine enkephalin, ANP)
- **Sweating, Headaches, Palpitations (50-75%)**
- **Pallor (flushing)**
- **Anxiety, Nervousness, Panic Attacks**
- **Nausea, Vomiting**
- **Attacks can last seconds to hrs and can be as infrequent as one every few months**

## Pheochromocytoma: Clinical Presentation (cont.)

- **May be associated with devastating consequences**
  - **Myocardial Infarction (Heart Attack)**
  - **Pulmonary Edema (Fluid in the Lungs)**
  - **Stroke (intracranial hemorrhage, emboli)**
  - **Circulatory Collapse (shock)**

## Pheochromocytoma: Metabolic Abnormalities

- **Lactic Acidosis**
- **Hypercalcemia (elevated calcium)**
- **Glucose Intolerance and Diabetes**
- **Associated Syndromes (ACTH, VIP)**

## Pheochromocytoma: Clinical Presentation

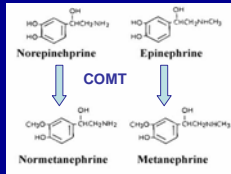
**Patients with pheochromocytoma can present with minor symptoms leading to misdiagnosis as essential hypertension, particularly in the elderly due to decrease sensitivity to catecholamines with age.**

- Mayo Clinic Series, 54 Cases Autopsy-Proven Pheochromocytoma (Sutton et al, 1981)
  1. Only 17% diagnosed correctly before death
  2. 54% hypertension
  3. 27% headaches
  4. 17% palpitations

## Pheochromocytoma: Biochemical Diagnosis

Diagnosis of pheochromocytoma based on establishing elevated levels of catecholamines or catecholamine metabolites in the urine or blood.

- Urine norepinephrine & epinephrine
- Urine normetanephrine & metanephrines
- Plasma norepinephrine & epinephrine
- Plasma normetanephrine & metanephrine



## Sensitivity and Specificity of Urine and Plasma Tests for Pheochromocytoma

Lenders et al, JAMA 287:1427, 2002 (NIH)  
Sawka et al, JCEM 88: 553, 2003 (Mayo Clinic)

Test	Sensitivity (%)	Specificity (%)
Urine NE/E	91	75
Urine Met/Normet	97	69
Plasma NE/E	92	72
Plasma Met/Normet	99	82

## Causes for False Positive Results for Catecholamines and Metanephrines

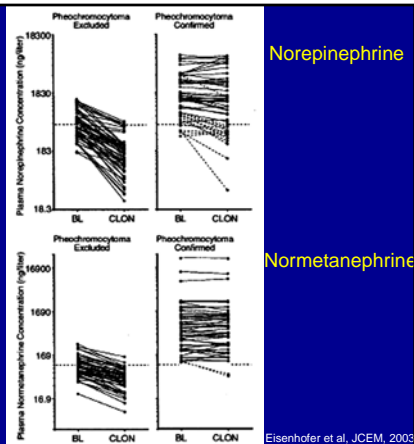
- **Age**
  - Increasing age associated with increasing levels metanephrines
- **Stress**
  - surgery, MI, CHF, CVA, DKA, sleep apnea
- **Dietary Interference and Smoking**
  - coffee (caffeic acid), caffeine, ETOH, nicotine
- **Medication**
  - tricyclic antidepressants and antipsychotics
  - theophylline
  - levodopa
  - drugs containing catecholamines (sudafed, amphetamines, albuterol)
  - withdrawal from clonidine
  - $\beta$ -blockers,  $\alpha$ -blockers, labetalol and sotalol
  - Acetaminophen (plasma metanephrines)

## General Guidelines for For Establishing Diagnosis

- If plasma or urinary fractionated metanephrines are 4x upper reference limit, dx pheo highly likely.
- Clonidine suppression test can help to establish the diagnosis of pheochromocytoma when there are equivocal elevations in plasma catecholamines and/or metanephrines.

## Clonidine Suppression Test

0.3 mg clonidine po;  
<40% decline 3h later compared to baseline



Norepinephrine

Normetanephrine

Eisenhofer et al, JCEM, 2003

## Familial Pheochromocytoma Is Associated With Specific Biochemical Phenotypes

	Multiple endocrine neoplasia type 2	von Hippel-Lindau syndrome	Sporadic
n	35	56	169
M/F	16/19	31/23	86/83
Mean age $\pm$ SD (years)	41.0 $\pm$ 12.2	47.3 $\pm$ 16.0	41.3 $\pm$ 15.8
Plasma-free normetanephrine (%) <sup>a</sup>	86	96	98
Plasma-free metanephrine (%) <sup>a</sup>	100	11	60
Plasma noradrenaline (%)	41	71	82
Plasma adrenaline (%)	44	4	43
Urinary normetanephrine (%)	100	95	94
Urinary metanephrine (%)	95	14	54
Urinary noradrenaline (%)	52	78	82
Urinary adrenaline (%)	58	2	38
Urinary vanilylmandelic acid (%)	63	36	77

Pacak et al, J Int Med 257:60, 2005

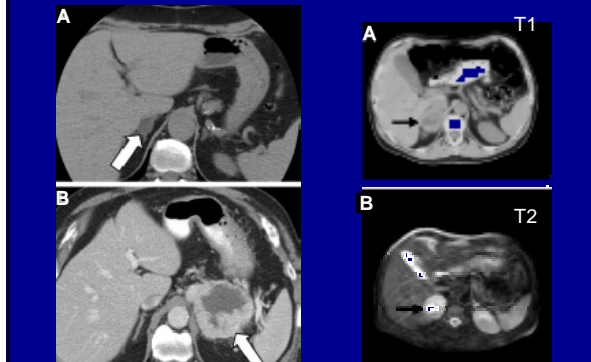
## Genetic Screening

- Available for 4 genes: VHL, RET, SDHD, SDHB
- Patients should be selected for screening on basis of those most likely to have a hereditary disease:
  - Age
  - Clinical manifestations in the patient or family members
    - Hypercalcemia, medullary thyroid carcinoma, retinal or brain hemangioblastomas; renal cell cancer
  - Type of catecholamine produced (normetanephrine)
  - Multiple lesions
  - Malignant lesions

## Pheochromocytoma: Radiologic Localization

- CT
- MRI

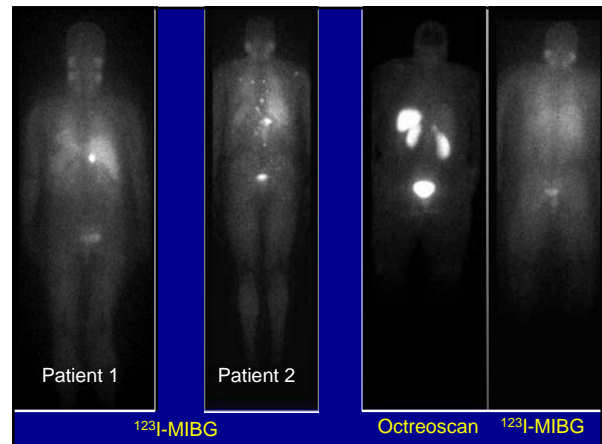
### Adrenal Adenoma vs Pheochromocytoma by CT Imaging



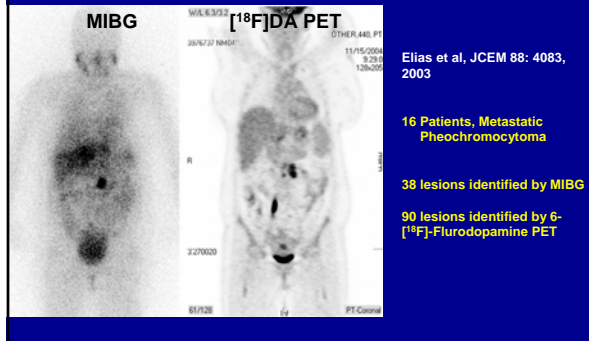
Abdominal CT and MRI do not prove functionality and are not particularly good at identifying paragangliomas or metastatic disease as may occur in the hereditary disorders.

## Pheochromocytoma: Radiologic Localization

- CT of chest and neck
  - Lacks specificity to identify mass as pheochromocytoma
- MRI of chest and neck
  - Lacks specificity to identify mass as pheochromocytoma
- $^{123}\text{I}$ -MIBG
- Octreoscan, [ $^{111}\text{In}$ -DTPA]-Octreotide
- 6- $^{18}\text{F}$  fluorodopamine PET



## PET Imaging of Pheochromocytoma

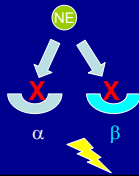


## Pheochromocytoma: General Management Goals

- Control B.P. (< 160/90)
- Induce orthostatic hypotension but not <80/45
- EKG without ischemic changes
- Control heart rate and heart rhythm

## Pheochromocytoma: Pharmacologic Management

- **Pharmacological Blockade**
  - Alpha Blockers
    - phenoxybenzamine (Dibenzyline), prazosin (Minipress), terazosin (Hytrin), doxazosin (Cardura)
  - Beta Blockers
    - Atenolol
  - Combination Blockers
    - Labetolol
  - Calcium Channel Blockers
  - Tyrosine Hydroxylase Inhibitors
    - metyrosine (Demser)



## Definitive Management of Pheochromocytoma is Surgical

## Malignant Pheochromocytoma

- Can not be diagnosed by assessment of the primary tumor and requires the presence of metastasis
- No effective cure
- Mortality ~50% at 5 yrs without treatment

## Malignant Pheochromocytoma: Treatment Options

- Pharmacological Blockade
- Surgery (tumor debulking)
- Cryoablation, Radiofrequency Ablation
- Chemotherapy (CVD, cytoxan / vincristine / dacarbazine q21d)
- <sup>131</sup>I-MIBG Radiotherapy

## SUMMARY

Based on key points from the  
First International Symposium on Pheochromocytoma,  
Nature Clinical Practice Endocrinology & Metabolism, 2007

- Plasma or urinary fractionated metanephrines are the most accurate screening procedures
- Localization studies should only follow reasonable clinical and/or biochemical evidence of a tumor; CT and MRI detect most tumors; functional imaging with <sup>123</sup>I-MIBG
- Genetic testing is not currently cost-effective for every gene in every patient, but age at diagnosis, type of catecholamine produced, presence of multiple tumors, family history and malignancy can be useful in deciding who should be tested and which genes to test.
- Laparoscopic surgery is the treatment of choice.
- Preoperative pharmacological blockade of adrenergic receptors is mandatory.
- Malignancy can not currently be diagnosed by assessment of primary tumor tissue and therefore, all patients with pheochromocytoma require continued observation following surgery for at least 5 years.