PHEOCHROMOCYTOMA

1905 poll coined the term
3-4/million in U.S. yearly
0.1% of hypertensive pt.
PHEOCHROMOCYTOMA

- Originates from
  1. adrenal medulla
  2. extraadrenal sympathetic paraganglia cells from skull base to bladder (9-23%) = para gangliomas

Neural crest cells migrate to para-aortic and paravertebral and along adrenal vein
PHEOCHROMOCYTOMA

Most extra-adrenal chromaffin cells regress
OOZ 75%
Mediastinum 10%
Bladder 10%
Head, Neck, Pelvis 5%
remoulness

Intraadrenal 77 patients (2 bilateral)
Extraadrenal 12 patients
Abdominal paraganglia-5
Organ of Zuckerkandl-6
Bladder-1

Children 11
7 d (63%), 4

Intraadrenal 6 patients (1 bilateral)
Extraadrenal 5 patients
Abdominal paraganglia-5
Organ of Zuckerkandl-3
Thorax-1

Organ of Zuckerkandl

Dizziness or faintness
Onset 10%
PHEOCHROMOCYTOMA

10% tumor

- Bilateral
- Malignant (26-35%)
- Multifocal
- Extraadrenal
- Children (30-43% extra, X-focal)
- Familial (50% bil.)
- Metastatic disease @ initial work up
PHEOCHROMOCYTOMA

15-20% in neuroectodermal tumor
VHL, VRH, TS
30-50% MEN 2
Bilateral and multifocal
Child with pheo.

1/3 bilateral. And familial

¼ sporadic have RET gene
PHEOCHROMOCYTOMA

Malignant pheo.

NO histologic, lab, clinical or imaging criteria from benign and malignant

Locoregional invasion / mets

Present where paraganglia cells are not present
PHEOCHROMOCYTOMA
“the great disguise”
Only ½ classic symptoms and signs
10% incidentaloma
Hx. Of HTN
refractory
new onset
paroxysmal
Recently excacerbated
PHEOCHROMOCYTOMA
“the great disguise”

TETRAD:
1. HTN
2. Headache
3. Sweating
4. Palpitations

Sp 93.8%
Sn 90.9%

Extensive differential
PHEOCHROMOCYTOMA
“the great disguise”

10% “pheocrisis”
No role for FNA
Metaneph., normeth., VMA (metabolites)
Epi : adrenal & OOZ (PNMT)
Biochemical diagnosis is often based on institutional experience.

Plasma metanephrines have high Sn & Sp (Mayo clinic, NIH, Vienna).

Because secretion may be episodic but metabolism is continuous i.e. leak.
PHEOCHROMOCYTOMA/
plasma metanephrines

Indicated in high risk and not in sporadic cases

Hereditary cases: Sn 97%
Sp 96%

Sporadic cases: Sn 99%
Sp 82%
<table>
<thead>
<tr>
<th>Plasma (nmol/liter)</th>
<th>Upper reference limit</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Hereditary</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Free metanephrines</td>
<td></td>
<td>97 (74/76)</td>
<td>99 (187/196)</td>
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<tr>
<td>Normetanephrine</td>
<td>0.6</td>
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</tr>
<tr>
<td>Metanephrine</td>
<td>0.3</td>
<td></td>
<td></td>
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<tr>
<td>Catecholamines</td>
<td></td>
<td>69 (52/75)</td>
<td>92 (126/137)</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>2.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.5</td>
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Sensitivity was calculated from patients with pheochromocytoma and false-negative test results for both normetanephrine and metanephrine.
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<td></td>
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<tr>
<td>Free metanephrines</td>
<td></td>
<td>97 (74/76)</td>
<td>99 (137/138)</td>
<td>96 (328/338)</td>
<td>82 (249/305)</td>
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<tr>
<td>Normetanephrine</td>
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<td></td>
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</tr>
<tr>
<td>Catecholamines</td>
<td></td>
<td>69 (52/75)</td>
<td>92 (126/137)</td>
<td>89 (303/389)</td>
<td>72 (220/304)</td>
</tr>
<tr>
<td>Norepinephrine</td>
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Sensitivity was calculated from patients with pheochromocytoma and false-negative test results for both normetanephrine and metanephrine from both NF and ENH. Sensitivity values in the table are calculated from the above results. Specificity was calculated...
<table>
<thead>
<tr>
<th>Urine (µmol/d)</th>
<th>Upper reference limit</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td>Hereditary</td>
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</tr>
<tr>
<td>Fractionated metanephrines</td>
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<td>96 (26/27)</td>
<td>97 (76/78)</td>
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<tr>
<td>Normetanephrine</td>
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</tr>
<tr>
<td>Women</td>
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<td>1.7</td>
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<tr>
<td>Men</td>
<td></td>
<td>3</td>
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<tr>
<td>Metanephrine</td>
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<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Catecholamines</td>
<td></td>
<td>79 (54/68)</td>
<td>97 (91/107)</td>
</tr>
<tr>
<td>NE</td>
<td></td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td></td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Total metanephrines</td>
<td></td>
<td>60 (27/45)</td>
<td>88 (61/69)</td>
</tr>
<tr>
<td>Vanillylmandelic acid</td>
<td></td>
<td>46 (30/65)</td>
<td>77 (66/58)</td>
</tr>
<tr>
<td>Biochemical Test</td>
<td>Sensitivity (%)</td>
<td>Specificity (%)</td>
<td>100% Specificity (%)</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Plasma metanephrine level</td>
<td>99</td>
<td>89</td>
<td>82</td>
</tr>
<tr>
<td>Plasma catecholamine</td>
<td>85</td>
<td>80</td>
<td>38</td>
</tr>
<tr>
<td>Urinary catecholamine</td>
<td>83</td>
<td>88</td>
<td>64</td>
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<tr>
<td>Urinary metanephrine</td>
<td>76</td>
<td>94</td>
<td>53</td>
</tr>
<tr>
<td>Urinary vanillylmandelic</td>
<td>63</td>
<td>94</td>
<td>43</td>
</tr>
</tbody>
</table>

Sensitivity was determined for tests in 151 patients with mainly sporadic pheochromocytoma, and specificity was determined for tests in 349 patients studied at the National Institutes of Health. Reprinted with permission from Pacak K, Linehan WM, Eisenhofer G, et al: Recent advances in genetics, diagnosis, localization, and treatment of
PHEOCHROMOCYTOMA

Combination of urinary total metanephries and cathecholamines indicating a specificity of 98% in Mayo
PHEOCHROMOCYTOMA

97% intraabdominal

One of few curable causes of hypertension

3 patterns

• Sustained
• Sustained with paroxysm
• Paroxysmal with intermittent normotension
PHEOCHROMOCYTOMA/LOCALIZATION STUDIES

Localization: combination of anatomic and functional studies

Adrenal masses 5-9% population

Most of which are benign, nonfunctional incidentalomas

6.5% are PHEO.
Can be always localized preop. Allowing a focused surgical approach without general abdominal exploration

*Noncontrast* CT rarely misses a lesion: 97% intraabdominal and >2 cm <10 HU
PHEOCHROMOCYTOMA/LOCALIZATION STUDIES

CT Sn adrenal 85-94%
extra 90%
Sp 70%
MRI 90% bright on T2 and have high water density (Test of choice in pregnant pt. And children)
It is also indicated in large tumors >6cm and large extraadrenal tumors to rule out any vascular invasion
Sn 93-100%, Sp 67%
PHEOCHROMOCYTOMA/LOCALIZATION STUDIES

MIBG NE ANALOG

Sn 80-90% (78%); Sp 100%
extraadrenal
multifocal
recurrent pheochromocytoma
less sensitive

Need to block thyroid
PHEOCHROMOCYTOMA/LOCALIZATION STUDIES

Sn 77-90%(78%)
Sp 95-100%
[¹⁸] FDG PET
SSRS(Octreoscan)
Pheochromocytoma suspected biochemically

Adrenal CT or MRI
(93%–100% sensitivity) (70% specificity)

Suspect pheochromocytoma in adrenal gland

Suspect extraadrenal pheochromocytoma

Whole-body CT/MRI

MIBG
(77%–90% sensitivity) (95%–100% specificity)

Adrenal pheochromocytoma; surgery

Adrenal incidentaloma or pheochromocytoma?

MIBG

Extraadrenal pheochromocytoma located; surgery

Consider false-positive biochemical test results

Possible pheochromocytoma; need independent confirmation

Positive results on repeated biochemical tests

PET/venous sampling/follow-up
Biochemically proven pheochromocytoma

Start with abdominal/pelvic CT/MRI

CT

MRI

Pheochromocytoma in different location

Perform chest and neck CT

Most likely pheochromocytoma

(+T2)

(-T2)

Pheochromocytoma in different location

Perform MRI of chest and neck (in pregnant women or children) or proceed to CT arm of algorithm

If no distorted anatomy found

If distorted anatomy found proceed to MRI (from neck to pelvis) and to functional imaging

Proceed to localize/confirm pheochromocytoma and to rule out metastatic disease

Regardless of anatomical imaging results proceed to functional imaging

[\textsuperscript{123}I/\textsuperscript{131}]MIBG\textsuperscript{*}

Pheochromocytoma confirmed; surgical or medical treatment to follow

PET with [\textsuperscript{18}F]-DA or [\textsuperscript{18}F]-DOPA

Consider unusual type of pheochromocytoma\textsuperscript{**} or malignant pheochromocytoma;

Perform Octreoscan or [\textsuperscript{18}F]-FDG PET;

If negative consider venous sampling coupled with measurement of plasma free metanephrines
PHEOCHROMOCYTOMA/
PERIOP. Mgmt

3 principles:
1. Rx. Of HTN
2. Expand intravascular volume
3. Control cardiac arrhythmias

PBZ long acting $\alpha$-antagonists 1-3 wks
Lessens risks of CV collapse when tumor is removed
Selective $\alpha$-1/Ca$^{+2}$ channel blockers
PHEOCHROMOCYTOMA/PERIOP. Mgmnt

- B-blockers: arrhythmia/extrasystoles
  - β blockade should not be started until adequate α-blockade leading to unopposed α effect:
    1. worsened vasoconstriction
    2. HTN crisis
    3. CHF(preexisting myopathy)
    4. Pulm. Edema
PHEOCHROMOCYTOMA/PERIOP. Mgmt

Avoid anesthetic drugs that precipitate cathecolamine secretion

A-line
CVP-Line
Nitroprusside: HTN episodes,
Esmolol: tachy, arrythmias
Phentolamine
PHEOCHROMOCYTOMA/PERIOP. Mgmnt

In the past, mortality was high as 50%
Currently :<5%
25 %pt. , the HTN is essential but may require less medical Rx.
PHEOCHROMOCYTOMA/
Surgical considerations

Pregnancy
Maternal MR 17%
Fetal MR 40%
1st trimester
Late in pregnancy : c-section
PHEOCHROMOCYTOMA/
Surgical considerations

MEN 2 (Bilateral and hyperplasia precedes development of pheo.)
If unil.: unil. adrenalectomy and close F/U for devpt. Of metachronous lesions 1/3
Bil. Adrenalectomy to prevent metachronous leaving pt. With 10-30% risk of addisonian crisis
PHEOCHROMOCYTOMA/
Surgical considerations

Cortical sparing with risk of recurrence of 25% in long term @10 yrs
PHEOCHROMOCYTOMA/
Surgical Approaches

1926 Charles Mayo
   Cesar Roux
1989 laparoscopy for cholelithiasis
1991 Snow et al. first transabdominal
1992 Gagner : first lateral
   lap.adrenalectomy
1995 Mercan posterior , retrop.
   laparoscopic
Box 37-5. Indications and Contraindications for Laparoscopic Adrenalectomy

- **Indications**
  - Aldosteronoma
  - Cushing’s syndrome
  - Cortisol-producing adenoma
  - Adrenal hyperplasia from failed treatment of ACTH-dependent Cushing’s syndrome
  - Primary adrenal hyperplasia
  - Pheochromocytoma (sporadic or familial)
  - Nonfunctioning cortical adenoma (>4–5 cm or atypical radiographic appearance)

- **Contraindications**
  - Any locally invasive adrenal tumor
  - Regional lymph node metastases
  - Large adrenocortical cancer
  - Existing contraindication to laparoscopic surgery
  - Prior nephrectomy, splenectomy, liver resection on affected side

- **Controversial**
  - Suspected primary adrenal malignancy
  - Large tumor size
  - Adrenal metastasis
PHEOCHROMOCYTOMA/ Surgical Approaches

6-8 cm as the limit for lap. Approach
Pre-op or intraop. evidence of malignancy
OPEN APPROACH: Malignant size

1. Anterior(extraadrenal,bil.,mets.)
2. Thoracoabdominal(large malignant)
3. Lateral
4. Posterior retroperitoneal
PHEOCHROMOCYTOMA/
Surgical Approaches

Very vascular: 3 arterial supplies:
  • Inferior phrenic
  • Aorta
  • Renal artery

Venous: single large
  right: short, IVC directly
  left: left renal vein
PHEOCHROMOCYTOMA/ Surgical Approaches

Mortality 0-3%
Morbidity <5%
Minimize tumor manipulation
PHEOCHROMOCYOTOMA/ FOLLOW UP CARE

No reliable method to distinguish benign from malignant: lifelong surveillance

RR benign 6.5 %

½ of malignant have residual disease

Recurrent pheo. may occur late as 20 yrs.
PHEOCHROMOCYTOMA/ prognosis

Nonmalignant pheo. 5 yr survival >95%
RR<10%
Resection cures HTN in 75%
25% better control 2° irreversible vascular and renal damage
PHEOCHROMOCYTOMA/
Surgical considerations

Malignant: 40% 10yr survival

debulked when possible

$^{131}$I MIBG small soft issue mets.

ERT Bony mets
PHEOCHROMOCYTOMA / Surgical Approaches

“FOCUSED APPROACH”
Laparoscopic adrenalectomy: gold standard
Decreased hospital stay
Less analgesic req.
Short convalescence
< blood transfusion
FEWER hemodynamic changes