Pheochromocytoma – pitfalls in diagnosis

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Faculty/Presenter Disclosure

- **Faculty:** Jacques Lenders

- **Relationships with commercial interests:**
  - Grants/Research Support: None
  - Speakers Bureau/Honoraria: None
  - Consulting Fees: None
  - Other: None
Pitfalls in diagnosis to be addressed:

• Medical history and physical examination

• Biochemical testing: exclusion / confirmation of excess catecholamine secretion

• Tumor location: anatomical and functional imaging
• Pheochromocytoma is still missed: 0.05 % in autopsy studies!
• Diagnostic delay for pheochromocytoma is ± 3 years!
• Timely and proper treatment: possible complete cure

therefore

Early consideration of tumor is key!!
SURGICAL REMOVAL OF TUMOR

MEDICAL HISTORY + PHYSICAL EXAMINATION

Clinical Clues!!

CONSIDER IT

DIAGNOSE and FIND IT

SURGICAL REMOVAL OF TUMOR

Hamilton 2014
### Signs and symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>headache</td>
<td>70-90%</td>
</tr>
<tr>
<td>palpitations</td>
<td>50-70%</td>
</tr>
<tr>
<td>Paroxysms</td>
<td>!</td>
</tr>
<tr>
<td>usually &lt; 30 minutes</td>
<td></td>
</tr>
<tr>
<td>spontaneous or elicited</td>
<td></td>
</tr>
<tr>
<td>paroxysmal</td>
<td>50%</td>
</tr>
<tr>
<td>orthostatic hypotension</td>
<td>10-45%</td>
</tr>
<tr>
<td>hyperglycemia</td>
<td>40%</td>
</tr>
</tbody>
</table>

*Paroxysms:*

- Usually < 30 minutes
- Spontaneous or elicited

*Headache:* 70-90%

*Palpitations:* 50-70%

*Paroxysms:* 50%
Spells /paroxysms may:

• occur spontaneously and/or
• be elicited by many factors like:
  • drugs* (e.g. dopamine receptor antagonists, corticosteroids, histamine)
  • anesthesia (drugs, intubation)
  • micturition
  • mechanical factors
  • foods

*Eisenhofer et al. Drug Safety 2007;30:1031
Pheochromocytoma

Production catecholamines

symptoms

Asymptomatic

Catastrophe
### Impact of prevalence (pre-test probability) on predictive value of test

<table>
<thead>
<tr>
<th>Prevalence (pre-test probability)</th>
<th>Neg pred. value</th>
<th>Pos pred. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 %</td>
<td>99.9 %</td>
<td>6 %</td>
</tr>
<tr>
<td>30 %</td>
<td>99 %</td>
<td>74 %</td>
</tr>
<tr>
<td>80 %</td>
<td>91 %</td>
<td>96 %</td>
</tr>
</tbody>
</table>

- **Sens**: Sensitivity (98%)
- **Spec**: Specificity (85%)
- **Neg pred. value**: Negative Predictive Value
- **Pos pred. value**: Positive Predictive Value

Hamilton 2014
### Differential diagnosis

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endocrine</strong></td>
<td>hyperthyreoidism / med. thyr. carc carcinoid</td>
</tr>
<tr>
<td></td>
<td>hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>menopausal</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td>heart failure / arrhythmias</td>
</tr>
<tr>
<td></td>
<td>ischemic heart disease</td>
</tr>
<tr>
<td></td>
<td>POTS</td>
</tr>
<tr>
<td><strong>Neurologic</strong></td>
<td>baroreflex failure</td>
</tr>
<tr>
<td></td>
<td>migraine</td>
</tr>
<tr>
<td></td>
<td>dienceph. autonomic epilepsia</td>
</tr>
<tr>
<td></td>
<td>meningioma</td>
</tr>
<tr>
<td></td>
<td>Guillain-Barre syndrome</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td>acute intermittent porphyria</td>
</tr>
<tr>
<td></td>
<td>panic disorder</td>
</tr>
<tr>
<td></td>
<td>mastocytosis</td>
</tr>
<tr>
<td></td>
<td>withdrawal alcohol / clonidine medication (factitious)</td>
</tr>
</tbody>
</table>
**DIAGNOSTIC WORK-UP**

*First: biochemical testing*

Demonstration of *excess* production of catecholamines or its metabolites in *plasma* or *urine*

*Second: imaging*
Catecholamines: **episodic** secretion

Metanephrines: **continuous** secretion
Which compound for initial testing in 2014?

**Metanephrines: highest diagnostic accuracy**

- **Plasma**  
  - Sens: 95-99%  
  - Spec: 89-98%

- **24 hour urine**  
  - Sens: 95-97%  
  - Spec: 86-95%

**Assays**

- HLPC-ECD or LC-MS/MS
- Immuno-assays not sufficiently validated!
Norepinephrine
Normetanephrine

Epinephrine
Metanephrine

URL Norepi
URL NMN

URL Epi
URL MN
Causes of a false-negative test result

- oxidative degradation because tubes not on ice (cats > mets)
- sampling 24-hours urine may be incomplete
- catecholamine secretion is episodic
- small tumors may be ‘silent’
Causes of a false-positive test result

- sampling conditions: after supine rest vs sitting without preceding rest

- elevations in catecholamines / metabolites are not specific for pheochromocytoma
  - increased sympathetic activity: e.g. heart failure, hypoglycemia etc
  - effects of diet constituents (methoxytyramine)
  - effects of renal function impairment (metanephrines 2-3 fold increased)
  - interfering effects of drug treatment
Sampling conditions for metanephrines

**BLOOD**
- preferably after 30 minutes of supine rest
- after fasting state (only for methoxytyramine)
- collect in heparinized tubes on ice

**URINE** (24-hours)
- in container without additives or evt sodiumbisulphite
- acidify urine in lab to pH 4 before storing
- also measure creatinine excretion
Normetanephrine: influence of posture

Plasma Normetanephrine (pmol/L)

Seated - rest

Supine + rest

p<0.001

<table>
<thead>
<tr>
<th></th>
<th>Plasma</th>
<th></th>
<th>Urine</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NMN</td>
<td>MN</td>
<td>NMN</td>
<td>MN</td>
</tr>
<tr>
<td>Acetaminophen*</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Labetalol*</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Sotalol*</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>α-methyldopa*</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Tricyclic antidepressants†</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Buspirone*</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Phenoxybenzamine†</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>MAO-inhibitors†</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Sympathomimetics†</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cocaine†</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Sulphasalazine*</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Levodopa‡</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

* Analytical interference with HPLC-ECD
† Pharmacodynamic interference
Excluded additional testing needed

Plasma level (nmol/L)

- Normetanephrine: Pheo 2.20, Excluded 0.61
- Metanephrine: Pheo 1.20, Excluded 0.31
Follow-up testing in case of slightly increased test results

- In about 20% of tested patients: false-positive test results (Yu et al. 2009)
- Only 28% of false-positive test results adequate follow-up (Anas et al. 2010)

So what to do as necessary follow-up?

• Try to stop interfering drug treatment
• Repeat testing (plasma metanephrines: after supine rest)
• Clonidine suppression test using plasma normetanephrine

Eisenhofer et al. J Clin Endocrinol Metab 2003;88:2656

Hamilton 2014
Anatomical imaging

sensitivity: 88-100%

specificity: 75-80%

1. CT scan

2. MRI
   - pregnancy / allergy
   - metastatic / HNPGL
   - germline mutations
Differential diagnosis adrenal mass

- incidentaloma (± 4% increases with age to 10%)
- benign adenoma (± SCS)
- pheochromocytoma
- adrenal cortical carcinoma (ACC)
- angiomyolipoma
- ganglioneuroma
- myelolipoma
- hemangioma
- granuloma
- metastasis
<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>CT Size</th>
<th>CT Homogeneous</th>
<th>CT Margins</th>
<th>CT Density</th>
<th>CT Abs. Washout</th>
<th>MRI T2-Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pheo</td>
<td>variable</td>
<td>variable</td>
<td>variable</td>
<td>most &gt;10 HU</td>
<td>&lt;60%</td>
<td>hyperintense</td>
</tr>
<tr>
<td>Adenoma</td>
<td>most &lt; 3 cm</td>
<td>+</td>
<td>smooth</td>
<td>70% has HU &lt; 10</td>
<td>&gt;60%</td>
<td>iso-intense</td>
</tr>
<tr>
<td>ACC</td>
<td>most &gt; 4 cm</td>
<td>-</td>
<td>irregular</td>
<td>most &gt;10 HU</td>
<td>&lt;60%</td>
<td>hyperintense</td>
</tr>
<tr>
<td>Metastasis</td>
<td>variable</td>
<td>-</td>
<td>irregular</td>
<td>most &gt;10 HU</td>
<td>&lt;60%</td>
<td>iso-hyper-intense</td>
</tr>
</tbody>
</table>
29% behaves as adenoma
Functional imaging ligands

- **68Ga-DOTA peptides**
- **111In-DTPA-pentetreotide**
- **18F-FDA**
- **123/131I-MIBG**

**SSTR**

**Internalization in endosomes**

- **18F-FDG-6P**
- **18F-FDG**

**VMAT**

**Noradrenaline**

**DBH**

**Dopamine**

**LAT**

**18F-FDOPA**

**GLUT**

**Dopa**

**68Ga-DOTA peptides**

**111In-DTPA-pentetreotide**

**18F-FDA**

**123/131I-MIBG**

**SSTR**

**Internalization in endosomes**

**VMAT**

**Noradrenaline**

**DBH**

**Dopamine**

**LAT**

**18F-FDOPA**

**GLUT**

**Dopa**
Purpose to determine:

1. multifocal / metastatic disease
2. determine potential treatment with $^{131}I$-MIBG

Diagnostic accuracy depends on:

1. germline mutation status
2. adrenal / extra-adrenal / metastatic
**False-positive MIBG uptake due to:**

1. Normal physiological uptake in adrenals (in 50-80%)
2. Hyperplasia after unilateral adrenalectomy
3. Other neuroendocrine lesions

**False-negative MIBG uptake due to:**

1. Small size
2. Necrosis
3. Dedifferentiation: loss of expression of transporters
4. Lack of VMAT transporters (HNPGLs)
5. Drugs that interfere with MIBG uptake
### Examples of drugs that may impair $^{123}$I-MIBG uptake

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenergic neurons blockers</td>
<td>Reserpine, labetalol</td>
</tr>
<tr>
<td>Sympathomimetic drugs</td>
<td>Ephedrine, norepinephrine, metaraminol</td>
</tr>
<tr>
<td>$\beta_2$ stimulants (sympathomimetics)</td>
<td>Salbutamol, terbutaline, eformoterol</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Amlodipine, diltiazem, nifedipine, verapamil</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Amitriptyline, nortriptyline, imipramine</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Haloperidol, clozapine, risperidone, sulpiride,</td>
</tr>
<tr>
<td>CNS Stimulants</td>
<td>Amphetamines, methylphenidate, caffeine</td>
</tr>
<tr>
<td>$\alpha$-adrenoceptor blockers</td>
<td>Phenoxybenzamine (intravenous doses)</td>
</tr>
<tr>
<td>only Opioid analgesics</td>
<td>Tramadol</td>
</tr>
</tbody>
</table>

**Drugs interfering with MIBG-uptake** Solanki et al. Nucl Med Commun 1992;13:513
SDHB-related metastatic PPGL

MEN2-related metastatic PPGL

18F-FDOPA 18F-FDG

18F-FDOPA 18F-FDG

Timmers et al. JCEM 2009;94:4757
Key home messages

- Consider pheochromocytoma in each patient with paroxysms
- First biochemical testing, then imaging
- Initial test: plasma or urinary metanephrines
- Blood sampling: preferably after fasting / >20 min. supine rest
- Don’t forget follow-up in patients with positive test result
- Check interfering medication when ordering $^{123}$I-MIBG scan
- Results of functional imaging depend on the genetic background
International collaboration

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University of Florence, Florence, Italy

Henri Timmers  
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Radboud University Medical Center, Nijmegen, The Netherlands

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To be presented at ENDO2014 in Chicago