بسم الله الرحمن الرحيم

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Pheochromocytoma: updates on management strategies

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INTRODUCTION
Pheochromocytoma (PCC) is a neuroendocrine tumor of the medulla of the adrenal glands (originating in the chromaffin cells) that secretes excessive amounts of Catecholamines, which are very powerful vasoactive hormones.
The estimated annual incidence is 2 to 8 per million person.

The average age at diagnosis is 24.9 years in hereditary cases and 43.9 years in sporadic cases.

Men and women equally affected.
• 10% Familial
• 10% Bilateral
• 10% Malignant
• 10% Extra adrenal
• 10% Children

- 40% attributed to genetic alterations.

- Hereditary syndromes have higher proportion of bilateral PCCs compared to sporadic occurrences.

- Malignant potential depends on the underlying mutation. (5% - 26%).

Based on biochemical secretory patterns, PCCs can be characterized into three different phenotypes:

- **Noradrenergic phenotype** predominantly produce norepinephrine.
- **Adrenergic phenotype** predominantly produce epinephrine.
- **Dopaminergic phenotype** predominantly produce dopamine.
Pheochromocytoma
68% sporadic

VHL 13%

MEN2 5%

NF1 4%

SDHD 4%

SDHB 6%

Genetic background

- Clusture of different genes have been implicated in the pathogenesis of these tumors; some of these represent inherited conditions.
- Cluster 1 are associated with abnormal HIF activation & overexpression of angiogenic factors. It includes mutations of:
  - VHL tumor suppressor gene
  - SDHB
  - SDHD

Bausch B, et al. JAMA Oncol. 2017
Cluster 2 is associated with abnormal activation of kinase-signaling pathways leading to abnormal cell growth and lack of apoptosis capacity. It includes mutations of:

- RET (rearranged during transfection) proto-oncogene.
- NF1 tumor suppressor gene.
Clinical presentation
Production catecholamines

Asymptomatic

symptoms

Catastrophe
Pheochromocytoma can manifest in many ways; specifically as sustained or paroxysmal HTN, episodes of palpitation, sweating, headache & anxiety.

Hypotension (orthostatic/paroxysmal) occurs in many patients:

- Intense α-adrenergic mediated vasoconstriction with volume contraction.
- β-adrenergic mediated vasodilatation.
- Tumor release of adrenomedullin (vasodilatory neuropeptide).
INVESTIGATIONS
Lab. Diagnosis:
- 24 hr urinary free metanephrines & catecholamines.
- Plasma metanephrines & catecholamines.
- Dynamic testing.
- Serum chromogranin A.
Tumor localization:
- CT, MRI
- MIBG SCAN
- PET
- CT/PET
- MRI/MIBG
Superior to urinary catecholamines & plasma catecholamines.

**False Positive:**
- Drugs: TCAs, labetalol, propanolol, opioids, MAO-i, dopa, amphetamines, cocaine, ethanol, sympathomimetics,
- Major physical stress (hypoglycemia, stroke,...) & OSA.

**False Negative:**
- Oxidative degradation (bec. tubes not on ice)
- Sampling 24 hr urine may be incomplete
- Small tumors may be silent

Plasma Catecholamines

- Drawn with patient fasting, supine, with an indwelling catheter in place > 30 min (SEN 85% SPEC 80%).

Plasma Metanephrines

- Not postural dependent (secreted continuously by pheo).
- Preferable in patients with renal insufficiency and in children (SEN 99% SPEC 89%).
- False Positive: acetaminophen.
Clonidine suppression test:
- Unlike normals, pheo patients have unsuppressed plasma norepinephrine with clonidine.
- May precipitate hypotensive shock!

Glucagon stimulation test:
- Pheo patients, will have a > 3x increase in plasma norepinephrine with glucagon.
- May precipitate hypertensive crisis!
Chromogranin A

- Storage vesicle protein that is co-stored & co-secreted with catecholamines.
- Elevated in 89% of PCCs.
- Serum Cg A in association with urinary metanephrines improves sensitivity of diagnostic and long-term follow-up testing & can detect recurrent PPCs.

Imaging

**CT abdomen**
- Adrenal pheo SEN 93-100%.
- >10 HU (lipid poor), avid contrast enhancement, and delayed washout

**MRI**
- More SEN than CT for extra-adrenal pheo
- SEN 77-90%  SPEC 95-100%
Localization: Nuclear medicine

- MIBG
- Octroscan (some pheo have somatostatin receptors)
- PET
Sensitivity for the detection of PCC (80% to 90%).

- Determine metastasis, paragangliomas, and evaluate for tumor recurrence.
False positive MIBG uptake:
- Hyperplasia after unilateral adrenalectomy.
- Normal physiological uptake of the adrenal glands (in 50-80%).
- Other neuroendocrine lesions.

False negative MIBG uptake:
- Small size.
- Necrosis.
- Drugs that interfere with MIBG uptake (Labetalol, reserpine, TCAs, phenothiazines).
- **CT-PET**
- **MRI-MIBG**
  - Detection & localization of tumors + function state
  - PGL
  - Metastasis
  - Recurrence
  - Therapeutic interventions efficacy.
DIAGNOSIS
- There is often diagnostic delay.
- Early consideration of the tumor is important.
The diagnosis of Pheochromocytoma depends mainly upon the demonstration of catecholamine excess by 24-h urinary metanephrines, plus tumor localization by multiphasic CT or by nuclear scanning following the biochemical confirmation.

<table>
<thead>
<tr>
<th>Urine tests</th>
<th>Presence of phaeochromocytoma</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Unlikely*</td>
</tr>
<tr>
<td>Catecholamines (HPLC)</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine (nmol/24 h)</td>
<td>&lt;500</td>
</tr>
<tr>
<td>Epinephrine (nmol/24 h)</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Fractionated metanephrines (HPLC)</td>
<td></td>
</tr>
<tr>
<td>Normetanephrine (nmol/24 h)</td>
<td>&lt;3000</td>
</tr>
<tr>
<td>Metanephrine (nmol/24 h)</td>
<td>&lt;1000</td>
</tr>
<tr>
<td>Total metanephrines (spectrophotometry)</td>
<td></td>
</tr>
<tr>
<td>Total of normetanephrine and metanephrine (μmol/24 h)</td>
<td>&lt;6</td>
</tr>
<tr>
<td>VMA (spectrophotometry)</td>
<td></td>
</tr>
<tr>
<td>VMA (μmol/24 h)</td>
<td>&lt;40</td>
</tr>
</tbody>
</table>
Differential diagnosis

- Carcinoid
- Menopause
- Hyperthyroidism
- Hypoglycemia
- Migrane
- Panic disorder
Screening for:

- MEN type 2A & 2B (50%).
- VHL (10-20%).
- Neurofibromatosis type 1 (2%).
- First degree relatives of the above diseases.
- Resistant hypertension (0.5%).
- Patients developing hypertensive crisis during surgery or general anaesthesia.

Genetic testing

- Bilateral, recurrent, or multifocal PCC.
- Paraganglioma (PGL).
- Family history of PGL/PCC.
Consensus Statement on next-generation-sequencing-based diagnostic testing of hereditary phaeochromocytomas and paragangliomas

The NGS in PPGL (NGSnPPGL) Study Group, Rodrigo A. Toledo1,2, Nelly Burnichon3,4, Alberto Cascon5, Diana E. Benn6, Jean-Pierre Bayley7, Jenny Welander8, Carli M. Tops9, Helen Firth10, Trish Dwight6, Tonino Ercolino11, Massimo Mannelli11, Giuseppe Opocher12, Roderick Clifton-Bligh6, Oliver Gimm13, Eamonn R. Maher10, Mercedes Robledo5, Anne-Paule Gimenez-Roqueplo3,4 and Patricia L. M. Dahia1

highly heritable tumours in humans1. Due to this high heritability, genetic testing has been recommended in all patients with PPGLs independent of a clear family history.
TREATMENT
Surgery

- Definite treatment of pheochromocytoma is surgical resection.
- Prior to 1951, reported mortality for excision of pheochromocytoma 24 - 50 % due to HTN crisis, arrhythmia, MI, stroke, hypotensive shock and multiorgan failure.
- Currently, mortality: 2 - 4 % (minimally invasive approaches, better periop. management)

Perioperative Management of pheo

**Preop:** Selective α1-blocker, α + β blockade, CCB.

**Intraop:** IV phentolamine, IV NTP, short acting BB.

**Postop:** Most cases can stop BP med. (75% normal BP & 25% have easily controllable BP, hypotension: IV crystalloid).

- 24h urine collection 2 wk postop.
- Urine catecholamines return to normal in 1 week.
Hypertensive crisis is controlled with IV phentolamine, nitroprusside, esmolol, labetalol.
Radiation therapy

Radionuclide treatment can be considered in patients with metastatic, surgically incurable or recurrent PCCs.

**131I-MIBG:** Better responses are seen in patients with limited disease & those with soft-tissue metastases.

**Radiolabelled somatostatin analogues:** Effective in reducing hormone secretion & determine tumor shrinkage, low toxicity.

**External radiation therapy** to areas (such as bone) where cancer has spread and cannot be removed by surgery.
Gene directed therapy

Interference with specific molecular targets along the oncogenic signaling pathways responsible both benign and malignant PCC gene mutations.

Ex: HIF inhibitors, VEGF inhibitors, mTOR inhibitor (everolimus) in combination with octreotide.

Prognosis

- HTN free: 5 years 74% & 10 years 45%.
- Tumor recurrence rates average around 10%.
- The presence of a SDHB mutation, and tumor size > 6cm are the most important predictors of recurrence.

R 3.1. We suggest follow-up for at least 10 years in all patients operated on for a PPGL to monitor local or metastatic recurrences or new tumours. High-risk patients (young patients and those with a genetic disease, a large tumour and/or a paraganglioma) should be offered lifelong annual follow-up. (⊕⊙⊙⊙⊙).
Special forms of PCCs
Malignant pheochromocytoma

- WHO defines malignant PCCs by the presence of metastases at sites where chromaffin tissue is not normally present (LNs, liver, lungs & bones).
- Malignant potential is found to be higher in PCCs with size >5 cm, PGLs and familial cases with mutations of succinate dehydrogenase subunit B (SDHB).
- Chemotherapy, MIBG irradiation, everolimus or sunitinib.
- Radiotherapy for bone metastasis

Pheo & Pregnancy

- PCC is a rare condition during pregnancy, the main clinical manifestation is HTN, also headache & palpitations can be presenting features.
- Usual time of presentation---labour----post partum.
- DD…eclampsia
- Diagnosis with 24h urine metaneph. & MRI.

1st trimester: Med. (Labetalol, Nifidipine, prazocin, hydralazine)

2nd trimester: Surgical resection of the tumour.

3rd trimester: Delivery is planned with concurrent or delayed adrenalectomy.

Asymptomatic pheo

- PCCs are increasingly being diagnosed during the work up of adrenal incidentalomas detected by abdominal imaging performed for other reasons.

- Asymptomatic adrenal mass was the initial presentation in 25% of cases in a recent series in USA.

- About 50% of PCCs are diagnosed only at autopsy because many of these tumors remain clinically silent during life.

Take Home Message
Consider PCC in each patient with:

- Paroxysms of hypertension with sweating, headache & palpitation.
- Family history.
- Genetic syndromes.

1st biochemical testing (urinary metanephrines) then tumor localization by imaging or radionuclide scan.
Check interfering medication before investigating (metanephrines, MIBG).

The only modality of curative treatment is tumor excision.

Proper peri-operative management improves the surgical outcomes.

Gene mutations are reported in 32-79% of cases, making genetic screening mandatory.

Gene directed therapy is hopefully a promising novel strategy for the treatment of PCC.
Thank you.