Phaeochromocytoma & PGL
clinical aspects, assessment & management

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Phaeochromocytoma & PGL
clinical aspects, assessment & management

- Diagnostics
- Treatment
- Guidance
- Clinical lens
Phaeochromocytoma & PGL
jonathan’s story

- Diagnostic testing
  - analyte
  - platform
Guidance
what we have

European Society of Endocrinology Clinical Practice Guideline for long-term follow-up of patients operated on for a phaeochromocytoma or a paraganglioma
Plouin PF, Amar L, Dekkers OM, Fassnacht M et al.

Pheochromocytoma and Paraganglioma: An Endocrine Society Clinical Practice Guideline
Lenders JWM, Duh Q-Y, Eisenhofer G et al.
Guidance methodology
grade system for recommendations

<table>
<thead>
<tr>
<th>Strength of recommendation</th>
<th>1</th>
<th>Strong</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>Weak</td>
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</table>

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>A</th>
<th>High</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>Very low</td>
</tr>
</tbody>
</table>

Guyatt GH et al. 2008.
GRADE: an emerging consensus on rating quality of evidence & strength of recommendations
British Medical Journal 336: 924-926.
Catecholamine metabolism candidate analytes in pheao-PGL

Tyrosine $\rightarrow$ Dopa $\rightarrow$ Dopamine $\rightarrow$ Norepinephrine $\rightarrow$ Epinephrine

Tyrosine Hydroxylase

Dopa

Dopamine $\rightarrow$ Norepinephrine

DBH

Norepinephrine $\rightarrow$ Metanephrine

PNMT

Metanephrine $\rightarrow$ Epinephrine

COMT

Epinephrine

VMA $\rightarrow$ MHPG $\rightarrow$ DHPG $\rightarrow$ Normetanephrine

MAO

Normetanephrine $\rightarrow$ MHPG $\rightarrow$ MHPG

MAO

MHPG

3-MT

HO

CH$_3$O

COOH

HO

CH$_3$O
Catecholamine metabolism

the value of metanephrines in diagnostics
## Analytes in diagnostic testing
### comparative performance

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Metadrenalines</td>
<td>98%</td>
<td>89%</td>
</tr>
<tr>
<td>Urine fractionated Mets</td>
<td>97%</td>
<td>72%</td>
</tr>
<tr>
<td>Urine Catecholamines</td>
<td>86%</td>
<td>88%</td>
</tr>
<tr>
<td>Plasma Catecholamines</td>
<td>84%</td>
<td>81%</td>
</tr>
<tr>
<td>Urine Total Mets</td>
<td>77%</td>
<td>93%</td>
</tr>
<tr>
<td>Urine VMA</td>
<td>64%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Sensitivity: 89%; Specificity: 88%

Lenders et al. 2002
JAMA 287:1427-1434
4 Referral Centres: 214 PC/PGL, 644 controls

Manchester Academic Health Science Centre
The University of Manchester

Manchester Academic Health Science Centre
The University of Manchester
ES clinical practice guideline

biochemical testing

- We recommend initial biochemical testing for PPGLs should include measurements of plasma free metanephrines or urinary fractionated metanephrines \(\text{1+:+:+:+} \)
- We suggest using liquid chromatography with MS or electrochemical detection methods rather than other laboratory methods \(\text{2+:+:+:+} \)
- We suggest drawing blood with the patient in the supine position & use of supine reference intervals \(\text{2+:+:+:+} \)
- We recommend that all patients with positive test results receive appropriate follow-up according to extent of increased values & clinical presentation \(\text{1+:+:+:+} \)

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Jonathan’s story
confirmation & localisation

- Plasma metanephrines
  - metanephrine 197 pmol/L (80-510)
  - nor-metanephrine 6386 pmol/L (120-180)

Functional imaging
123I-MIBG
We recommend imaging studies be initiated once clear biochemical evidence of a PPGL.

We suggest CT rather than MRI as first-choice modality because of excellent spatial resolution for thorax, abdomen & pelvis.

We recommend MRI in following patient groups:
- metastatic PPGL
- skull base & neck PGLs
- surgical clips that cause artifacts with CT & allergy to CT contrast
- where radiation exposure should be limited
  - children, pregnant women, known germline mutations & recent excessive radiation exposure

We suggest $^{123}$I-MIBG scintigraphy in patients with metastatic PPGL detected by other imaging modalities:
- when radiotherapy using $^{131}$I-MIBG is planned
- in some patients with an increased risk for metastatic disease
  - large size of primary, extra-adrenal, multifocal disease (except skull base & neck PPGLs)

We suggest $^{18}$F-FDG PET/CT in patients with metastatic disease:
- $^{18}$F-FDG PET/CT is preferred over $^{123}$I-MIBG
Catecholamine metabolomics
stratifying disease by biochemical profile

Tyrosine → Dopa → Dopamine → 3-Methoxytyramine

Malignant Catecholamine metabolome

Tyrosine: $\text{CH}_3\text{O}$
Dopa: $\text{HO}$
Dopamine: $\text{R}$
3-Methoxytyramine: $\text{CH}_3\text{O}$
We recommend defining malignancy of phaeochromocytoma & paraganglioma (PPGL) as the presence of metastasis in lymph node or other distant sites.

We suggest screening for metastatic tumours by [18F]-FDG PET/CT, if possible preoperatively:

- in patients with paragangliomas
- in patients with phaeochromocytomas & elevated (i.e. above the reference) levels of 3-methoxytyramine (3MT) in plasma or urine
- in patients carrying germ line mutations of the SDHB gene

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Jonathan’s story
added value of metabolomics

- **Plasma metanephrines**
  - metanephrine 197 pmol/L (80-510)
  - nor-metanephrine 6386 pmol/L (120-180)
  - 3-methoxytyramine 1.2 pmol/L
ES clinical practice guideline
peri-operative medical management

- We recommend all patients with hormonally functional PPGL undergo preoperative blockade 1★★★★
- We suggest α-adrenergic receptor blockers as first choice 2★★★★
- We recommend preoperative medical treatment for 7-14 days 1★★★★
  - normalize blood pressure & heart rate
  - include a high-sodium diet & fluid intake to reverse catecholamine-induced blood volume contraction preoperatively to prevent severe hypotension after tumour removal
- We recommend monitoring BP, HR & blood glucose levels with adjustment of associated therapies in the immediate postoperative period 1★★★★
- We suggest measuring plasma or urine metanephrines to diagnose persistent disease; & lifelong annual biochemical testing to assess for recurrent or metastatic disease 2★★★★
We recommend minimally invasive adrenalectomy (eg. laparoscopic) for most adrenal phaeochromocytomas 1

We recommend open resection for large (eg. 6 cm) or invasive phaeochromocytomas 1

- ensure complete tumour resection
- prevent tumour rupture & avoid local recurrence

We suggest open resection for PGLs, but laparoscopic resection can be performed for small, non-invasive PGLs in surgically favourable locations 2

We suggest partial adrenalectomy for selected patients to spare adrenal cortex & prevent permanent hypocortisolism 2

- hereditary phaeochromocytoma
- small tumours who have already undergone a contralateral complete adrenalectomy
Jonathan’s story
chance or predisposition......
Phaeochromocytoma/PGL

Genetic predisposition is less rare we thought

- **Syndromes & context**
  - familial paraganglioma
  - VHL
  - MEN2
    - RET
  - NF-1
  - Carney complex
  - TMEM127

- **Prevalence**
  - 15-28%
  - age dependent
  - phenotype-dependent
ES clinical practice guideline

We recommend that all patients with PPGLs should be engaged in shared decision making for genetic testing 1

We recommend the use of a clinical feature-driven diagnostic algorithm to establish the priorities for specific genetic testing in PPGL patients with suspected germline mutations 1

We suggest that patients with PGL undergo testing of SDH mutations & that patients with metastatic disease undergo testing for SDHB mutations 2

We recommend that genetic testing for PPGL be delivered within the framework of health care Ungraded
  - pretest and post-test counseling should be available
  - genetic testing should be performed by accredited laboratories

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Jonathan’s story
predisposition gene testing

- SDHD
  - C.278_280dup
  - duplication Tyrosine
  - SVUS
Molecular basis of SDHx PGL
the SDH complex

- SDH & mitochondrial function
  - electron transport chain & TCA cycle
- SDH complex structure
Proteomics in phaeo-PGL

SDHx-associated PGLs do not express SDHB

- **Rationale**
  - SDH complex stability
    - SDHB not expressed in SDHx mutations

- **Utility**
  - supporting genetic testing
    - variants uncertain significance
Jonathan’s story

integrated diagnostics

- SDHD
  - C.278_280dup
  - duplication Tyrosine

-SDHB expression
We recommend assaying plasma or urinary MN & 3MT every year to screen for local or metastatic recurrences or new tumours.

We suggest assaying plasma CGA levels every year in patients operated on for MN-negative, 3MT-negative & CGA-positive PPGL to screen for local or metastatic recurrences or new tumours.

We suggest performing imaging tests every 1–2 years in patients with biochemically inactive PPGL to screen for local or metastatic recurrences or new tumours.

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ESE Clinical Practice Guideline

duration of follow up

- We suggest follow-up for at least 10 years in all patients operated on for a PPGL to screen for 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.

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MDTs
the role specification

- Dealing with incomplete & imperfect information
- Managing uncertainty
- Dealing with risk
- Working with complexity
- Taking responsibility
We recommend that patients with PPGLs should be evaluated & treated by MDTs at centres with appropriate expertise to ensure favourable outcome  Ungraded recommendation

- patients should be referred to such centres in following situations
  - pregnancy
  - metastatic disease
  - issues concerning the complexity or difficulty in biochemical diagnosis; localization; performance and interpretation of genetic testing; preoperative preparation; surgical treatment; and follow-up

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- Guidance
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- Thanks
  - Bob Peaston
  - Chris Boot
  - ACB

The Association for Clinical Biochemistry & Laboratory Medicine
Better Science, Better Testing, Better Care
Phaeochromocytoma & PGL
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The Association of Clinical Biochemistry & Laboratory Medicine
Better Science, Better Testing, Better Care
National audit meeting, Royal College of Pathologists, September 2019