Pediatric Pheochromocytoma/Paraganglioma (PPGL)

Steven G. Waguespack, MD
Professor

Dept. of Endocrine Neoplasia and Hormonal Disorders
Department of Pediatrics-Patient Care
Disclosures:

None
Objectives

• Discuss the clinical presentation of PPGL in children, including the most common hereditary syndromes
• Highlight differences between children and adults with PPGL
• Discuss the diagnosis and treatment of pediatric PPGL, including metastatic disease
Chromaffin Cell Tumors*

*PHEO and sympathetic/functional PGL arise from chromaffin cells; parasympathetic or non-functional PGL are known as non-chromaffin paragangliomas
Parasympathetic PGLs

- Historically called “glomus tumors” or “chemodectomas”
- 1-3% functional
- Anatomic tumor locations
  - Glomus tympanicum/jugulare or jugulotympanic
    - middle ear mass, tinnitus, hearing loss
  - Vagal
    - neck mass, dysphagia, hoarseness
  - Carotid body
    - neck mass, cranial nerve palsy
  - Aortopulmonary body
    - none, unless large enough to cause pain or shortness of breath
Parasympathetic PGLs

Glomus tympanicum (middle ear PGL)

Glomus caroticum (carotid body PGL)
Sympathetic PGLs

- Most hypersecrete catecholamines
- Posterior mediastinum and abdomen/pelvis
  - Organs of Zuckerkandl
PPGL in Children

- Very rare--Incidence of 2/million/year
- 0.8-1.7% of hypertensive children
- 13% of all PPGL with childhood presentation
- Average age of diagnosis 13 years
- Extra-adrenal (up to 60%) & bilateral (10-25%)
- Up to 80% hereditary
- More likely to be metastatic (esp. PGL)

# PPGL: Children vs Adults

## Table 1. Demographic and Tumor Characteristics of Pediatric and Adult Patients With PPGLs

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pediatric</th>
<th>Adult</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 95</td>
<td>N = 653</td>
<td></td>
</tr>
<tr>
<td>Age at initial diagnosis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13.3 ± 3.5</td>
<td>44.7 ± 14.4</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>55.8% (53/95)</td>
<td>48.1% (314/653)</td>
<td>0.0980</td>
</tr>
<tr>
<td>Primary tumor locations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solitary adrenal</td>
<td>22.1% (21/95)</td>
<td>56.2% (367/653)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Solitary extra-adrenal</td>
<td>33.7% (32/95)</td>
<td>21.6% (141/653)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bilateral adrenal</td>
<td>11.6% (11/95)</td>
<td>8.7% (57/653)</td>
<td>0.2020</td>
</tr>
<tr>
<td>Multifocal&lt;sup&gt;b&lt;/sup&gt;</td>
<td>32.6% (31/95)</td>
<td>13.5% (88/653)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hereditary cases&lt;sup&gt;c&lt;/sup&gt;</td>
<td>80.4% (74/92)</td>
<td>52.6% (273/519)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Recurrent primary tumors&lt;sup&gt;d&lt;/sup&gt;</td>
<td>29.5% (28/95)</td>
<td>14.2% (93/653)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>49.5% (47/95)</td>
<td>29.1% (190/653)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No. N/D phenotype</td>
<td>93.2% (68/73)</td>
<td>57.3% (337/588)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Abbreviations: N/D, noradrenergic/dopaminergic.

<sup>a</sup> Age is shown as mean ± standard deviation.

<sup>b</sup> Multifocal locations indicate multiple extra-adrenal tumors or extra-adrenal and adrenal tumors but exclude bilateral adrenal tumors unless accompanied by one or more extra-adrenal tumors.

<sup>c</sup> Results were retrieved from 611 patients who underwent genetic testing.

<sup>d</sup> Recurrent primary tumors are defined as recurrences at an original site of tumor resection as well as new primary tumors at other locations a year or more after diagnosis of the first primary tumor.

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PPGL in Children—Clinical Presentation

- 70-90% present with HTN, usually sustained (up to 2% of hypertensive children)
- Sweating, visual problems, weight loss, nausea/vomiting, and polyuria/polydipsia
- Decreased school performance & behavioral problems
- Classic triad (paroxysmal sweating, HA, palpitations) uncommon
- Symptoms less common in inherited tumors
# PHEO/PGL—Signs & Symptoms

## TABLE 1. Pheochromocytoma: Clinical findings according to age

<table>
<thead>
<tr>
<th></th>
<th>&lt;20</th>
<th>&gt;20</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained</td>
<td>93%</td>
<td>68%</td>
</tr>
<tr>
<td>Without paroxysms</td>
<td>63%</td>
<td>58%</td>
</tr>
<tr>
<td>With paroxysms</td>
<td>37%</td>
<td>42%</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>7%</td>
<td>26%</td>
</tr>
<tr>
<td>Normotension</td>
<td>0</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Other symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>95%</td>
<td>90%</td>
</tr>
<tr>
<td>Sweating</td>
<td>90%</td>
<td>92%</td>
</tr>
<tr>
<td>Visual disturbances</td>
<td>80%</td>
<td>47%</td>
</tr>
<tr>
<td>Neurologic signs</td>
<td>65%</td>
<td>57%</td>
</tr>
<tr>
<td>Tachycardia, dysrhythmias</td>
<td>35%</td>
<td>72%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>15%</td>
<td>72%</td>
</tr>
</tbody>
</table>
Pediatric PPGL

Most Common

VHL - PHEO
SDHB - PGL
SDHD
RET
NF1
TMEM127
MAX
SDHC, SDHA, SDHAF2

Germline mutations found in 80% of children

Least Common

Others*

*FH, IDH1, HIF2A/EPAS1, PHD1 and PHD2, MDH2, KIF1β, MEN1

Parent of origin effects; clinical disease not present in children of females

Dahia P Nature Reviews Cancer 2014; Neumann HP NEJM 2002; Neumann HP Endo Rel Cancer 2017, Pamporaki JCEM 2017
CNS Hemangioblastoma
80%

Retinal Hemangioblastoma
85%

Pheochromocytoma
20-30%

Renal Carcinoma
40+%  

Pancreatic NET
11-17%

Endolymphatic Sac Tumors
4%

Epididymal Cystadenoma
60% of males

Figure Courtesy of Gilbert J. Cote, PhD
Inactivating mutations in $SDHx$, leading to dysfunction of complex II in the electron transport chain

Hereditary Paraganglioma Syndromes:

- PGL1 ($SDHD$)
- PGL2 ($SDHAF2$)
- PGL3 ($SDHC$)
- PGL4 ($SDHB$)
- PGL5 ($SDHA$)

Higher rate of malignancy

Petri et al
British Journal of Surgery
2009 96:1382
**SDHx-associated Tumors**

**UNCOMMON**
- (d) Pituitary adenoma (rare)
- (e) Renal cell carcinoma
- (f) GIST

**COMMON**
- (a) Head and neck PGL
- (b) Phaeochromocytoma
- (c) Abdominal PGL

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Benn DE et al., *Endocr Relat Cancer*. 2015
**SDHx and VHL**

**B. VHL: Pseudohypoxia**

The VHL Complex Disrupted

**Induction of hypoxic response under normoxic conditions (pseudo-hypoxia)**

- VEGF
- Glut1
- PDGF, TGFα

Angiogenesis
Glucose Transport
Autocrine Growth Stimulation

**References**

Bardella et al. *Biochimica et Biophysica Acta* 1807 (2011) 1432–1443

Bratslavsky et al. *Clin Cancer Res* 2007;4667 13(16)
MEN2A

- Medullary Thyroid Carcinoma (MTC) (> 90%)
- Parathyroid Neoplasia (0-20%)
- Pheochromocytoma (0-50%)

RET Figure adapted from Waguespack et al. Nat Rev Endocrinol. 2011 Aug 23;7(10):596-607

RET tyrosine kinase receptor
MEN2B

- Medullary Thyroid Carcinoma (MTC) (100%)
- MEN2B Phenotype (100%)
- Pheochromocytoma (~50%)

RET Figure adapted from Waguespack et al. Nat Rev Endocrinol. 2011 Aug 23;7(10):596-607
**NF1**

- Visual Impairment/Blindness
- Optic Gliomas
- Lisch Nodules
- Speech Impairments

**Skin:**
- Café-au-lait spots and/or neurofibromas (tumors) of varying sizes may occur anywhere.
- Scoliosis

**Digestive tract:**
- NF may cause pain, vomiting, chronic constipation or diarrhea.

**Seizures**
**Headaches**
**Brain Tumors**
**Bone Blood Vessel Defects**
**Learning Disabilities**
**Mental Retardation**
**Microencephaly** (oversized head)

**High blood pressure**
**Freckling where skin meets skin (armpits, groin, under breasts)**
**Early or delayed puberty**

**Other complications may include delay in learning to talk or walk; short stature, poor school performance, increase in size and number of tumors during pregnancy; severe itching, psychosocial burdens, and cancer.**

**Pseudarthrosis (false joints)**
**Bone deformities**

© NF, Inc. 2004

**MEN1**

**Anterior Pituitary Adenomas**
- 30-40%

**Parathyroid Hyperplasia**
- > 97%

**Duodenopancreatic Neuroendocrine Tumors**
- 75%

**PHEO** 2-6%; adult onset
- Screen pts with HTN

**Very rare; adult onset**
- Screen pts with HTN, adrenal mass
Other Genes Implicated in Hereditary PPGL

- **TMEM127**
- **MAX**
- **FH**
- **HIF2A** (aka EPAS1)
- **PHD1** and **PHD2** (aka EGLN2 and EGLN1)
- **BAP1**
- **KIF1β**
- **MDH2**

- Incomplete penetrance of PPGL
  - Typically adult onset
  - Few cases published
  - Screening guidelines not well established

1. Somatic mutations in cyanotic congenital heart disease
2. Associated with polycythemia

Muth J Intern Med 2019; Neumann Endocrine Related Cancer 2018; Eisenhofer Clin Biochem Rev 2017
Parent-of-Origin Effects in **SDHD** and **SDHAF2** (and possibly **MAX**)

Pedigree courtesy of Samuel Hyde, MMSc, CGC
VHL and SDHx tumors are noradrenergic (Cluster 1; pseudohypoxia)

MEN, NF1, and sporadic tumors are adrenergic (Cluster 2; tyrosine kinase signaling)

Difference in expression of PNMT

## Hereditary PPGL Screening

<table>
<thead>
<tr>
<th>Gene</th>
<th>Typical Age to Start</th>
<th>Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>RET</td>
<td>11-16(^1)</td>
<td>Annual Metanephrines(^2)</td>
</tr>
<tr>
<td>SDHB</td>
<td>5</td>
<td>Annual Metanephrines(^2), Annual Catecholamines(^3), Annual Chromogranin A Periodic Imaging(^4,5)</td>
</tr>
<tr>
<td>VHL</td>
<td>5</td>
<td>Annual Metanephrines(^2), Periodic Imaging(^4,6)</td>
</tr>
</tbody>
</table>

\(^1\) Depends on the specific RET mutation; age 11 years for 634, 883 and 918, and age 16 years for others

\(^2\) Plasma free metanephrines or urinary fractionated metanephrines

\(^3\) Consider 3-methoxytyramine if a dopamine secreting tumor is suspected

\(^4\) Avoid ionizing radiation for screening purposes

\(^5\) Abdominal/pelvis US in very young patients; Whole body MRI every 2 years in older patients

\(^6\) Abdominal US or MRI done in conjunction with imaging for other tumors

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PHEOs Identified by Screening are Smaller and Less Symptomatic

PHEO/PGL- Diagnosis

Measurement of plasma and/or 24 urine fractionated metanephrines (metanephrines + normetanephrines)

Waguespack and Fishbein Sperling 5th ed.
PPGL- Diagnosis

Clinical Suspicion of PHEO/PGL → Fractionated plasma or 24 hour urine metanephrines

- >4X ULN urine or >2x ULN plasma
- >ULN and <4X ULN urine or <2x ULN plasma
- ≤ULN

* Anatomic Imaging (CT or MRI):
  1) Abdomen/Pelvis; if negative,
  2) Neck/Chest

Repeat under optimized conditions & include catecholamines

Repeat if clinical suspicion remains high

Monitor & assess for other etiologies

Consider functional imaging if PGL or concern for multifocal primary disease or metastatic disease

Functional Imaging:
1) 68Ga-DOTATATE PET/CT or 123I-MIBG scan
2) If above is unavailable, consider [18F]-FDG PET/CT

1) Genetic counseling & testing
2) Consider chromogranin A
3) Surgery
4) Clinical follow-up for life

#Rule out interfering medications, over the counter supplements/herbs, recreational drugs, dietary or exercise influences, and improper collection procedures.

Possible false positive

Repea evaluation prn

Waguespack and Fishbein, Sperling 5th ed.
Anatomic Imaging for PHEO/PGL

CT

Vascular Tumors that enhance significantly after IV contrast

MRI

Hyperintense on T2-weighted images

Can be cystic/hemorrhagic

Waguespack and Fishbein, Sperling 5th ed
Functional Imaging for PPGL

- **Scintigrapy**
  - $^{123}$I-MIBG
  - $^{111}$In-Octreotide

- **PET**
  - $^{18}$F-FDG
  - $^{68}$Ga-DOTATATE
  - $^{18}$F-DOPA

Hofman and Hicks *Clin Cancer Res* 2015
Functional Imaging for PHEO/PGL

- $^{123}$MIBG scan

MEN2a and Bilateral PHEOS
Functional Imaging for PHEO/PGL

- $^{18}$FDG PET/CT
- $^{68}$Gallium Dotatate PET/CT

Figure Adapted from Velikyan, Theranostics 2014

Waguespack and Fishbein, Sperling 5th ed., In press
# PHEO/PGL - Pre-op Medical Management

## TABLE 14-3 Preoperative Medical Management of Pheochromocytoma/Sympathetic Paraganglioma

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Initial Pediatric Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-adrenergic receptor blockers</td>
<td>Doxazosin</td>
<td>α₁-antagonist</td>
<td>0.5-1 mg daily</td>
</tr>
<tr>
<td></td>
<td>Phenoxybenzamine</td>
<td>α₁- and α₂-antagonist</td>
<td>0.2-0.5 mg/kg/day divided BID (max 10 mg BID)</td>
</tr>
<tr>
<td></td>
<td>Prazosin</td>
<td>α₁-antagonist</td>
<td>0.05-0.1 mg/kg/day divided TID (max 1 mg TID)</td>
</tr>
<tr>
<td>β-adrenergic receptor blockers</td>
<td>Atenolol</td>
<td>β₁-antagonist</td>
<td>0.5-1 mg/kg/dose daily (max 50 mg daily)</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
<td>β₁-antagonist</td>
<td>1-2 mg/kg/day divided BID (max 50 mg BID)</td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
<td>β₁- and β₂-antagonist</td>
<td>0.5-1 mg/kg/day divided BID (max 40 mg BID)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Nifedipine (sustained release)</td>
<td>Calcium channel blocker</td>
<td>0.25-0.5 mg/kg/day or BID (max 60 mg total daily dose)</td>
</tr>
<tr>
<td>Inhibitors of catecholamine synthesis</td>
<td>Metyrosine</td>
<td>Tyrosine hydroxylase inhibitor</td>
<td>125-250 mg divided BID-TID</td>
</tr>
</tbody>
</table>

Surgery

- Open Adrenalectomy
  - Large PHEOs
- Laparoscopic Adrenalectomy
  - Anterior transperitoneal
  - Posterior retroperitoneal

Cortical-Sparing Adrenalectomy

- In MEN1, MEN2, and VHL\(^1\):
  - 7% recurrence in cortical-spared remnants
  - steroid independence in 78% at 3 years

- In MEN2A\(^2\):
  - 3% recurrence
  - 57% steroid independence

- In MEN2B\(^3\):
  - 10% recurrence
  - 62% steroid independence

Lifelong Follow Up Required

- September 1996, age 15
- August 2012, age 31

Refractory HTN during pregnancy

![Imaging of PGL and 18F-FDG PET/CT](image)
Metastatic PPGL

• No histological, biochemical, molecular, or genetic characteristics that predict malignant potential
• PGL>PHEO
• Sympathetic>Parasympathetic
• PPGL > 5cm; sympathetic PGL regardless of size
• SDHB+

Dahia et al. Endocr Relat Cancer. 2020 Aug;27(8)
Chemotherapy

- Cyclophosphamide, vincristine, and dacarbazine (CVD)

Theranostics

https://uihc.org/health-topics/what-theranostics
Radiopharmaceutical Options

- I-131 MIBG (Azedra®)

- Lu-177 DOTATATE (Lutathera®)
Ga 68 dotatate scan  

Iobenguane I131 scan
High-Specific-Activity $^{131}$I-MIBG

AZEDRA was proven to reduce the need for antihypertensive medication

- **Primary endpoint**
  - Reduction or discontinuation of antihypertensive medication by at least 50% for at least six months
  - 25% of patients treated with AZEDRA achieved the primary endpoint (n=17/68, 95% CI: 16–37%)

AZEDRA was shown to reduce the size of tumors

- **Secondary endpoint**
  - Overall tumor response, assessed radiographically per RECIST 1.0
  - 22% of patients treated with AZEDRA achieved a partial response (n=15/68, 95% CI: 14–33%)
  - 53% of responders experienced durable tumor responses lasting 6 months or longer

N=68; median age 55 yr (16-76; 1<age 18)

---

<table>
<thead>
<tr>
<th>AE by preferred term</th>
<th>Treatment-related AE, all grades</th>
<th>Treatment-related AE, grades 3-5</th>
<th>Any AE, all grades</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>52 (78)</td>
<td>1 (1)</td>
<td>53 (78)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>49 (72)</td>
<td>28 (41)</td>
<td>49 (72)</td>
</tr>
<tr>
<td>Anemia</td>
<td>40 (60)</td>
<td>14 (21)</td>
<td>43 (62)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>41 (60)</td>
<td>28 (41)</td>
<td>41 (60)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32 (47)</td>
<td>7 (10)</td>
<td>41 (60)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>39 (57)</td>
<td>26 (38)</td>
<td>39 (57)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>33 (49)</td>
<td>1 (1)</td>
<td>36 (53)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>27 (40)</td>
<td>0</td>
<td>28 (41)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>16 (24)</td>
<td>1 (1)</td>
<td>27 (40)</td>
</tr>
<tr>
<td>Headache</td>
<td>15 (22)</td>
<td>0</td>
<td>21 (31)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>8 (12)</td>
<td>1 (1)</td>
<td>18 (26)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14 (21)</td>
<td>1 (1)</td>
<td>17 (25)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11 (16)</td>
<td>2 (3)</td>
<td>16 (24)</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (6)</td>
<td>1 (1)</td>
<td>16 (24)</td>
</tr>
</tbody>
</table>

Data are numbers followed by percentages in parentheses.

- Grade 1 = mild AE; grade 2 = moderate AE; grade 3 = severe AE; grade 4 = life-threatening or disabling AE; grade 5 = death related to AE.

Source:

Systemic approaches to metastatic PPGL

Jasim and Jimenez Best Practice & Research Clinical Endocrinology & Metabolism 34 (2020)
Summary

• Pediatric PPGL are rare tumors that account for up to 2% of children with hypertension
• PPGL of childhood onset are more likely to be hereditary (cluster 1), noradrenergic, and multifocal/bilateral
• The major genetic syndromes in childhood are VHL and the familial paraganglioma syndromes (SDHx mutations)
• Malignancy risk is high (primarily due to SDHB mutations) and lifelong FU required for metachronous and metastatic disease
• Prospective screening typically incorporates labs and imaging (MRI); recommendations are primarily based on expert opinion
Thank You!

I am...

PHEO PARA
PHEAR LESS

pheopara.org