# PHEO PARA 101

Whitney Goldner, MD

University of Nebraska Medical Center

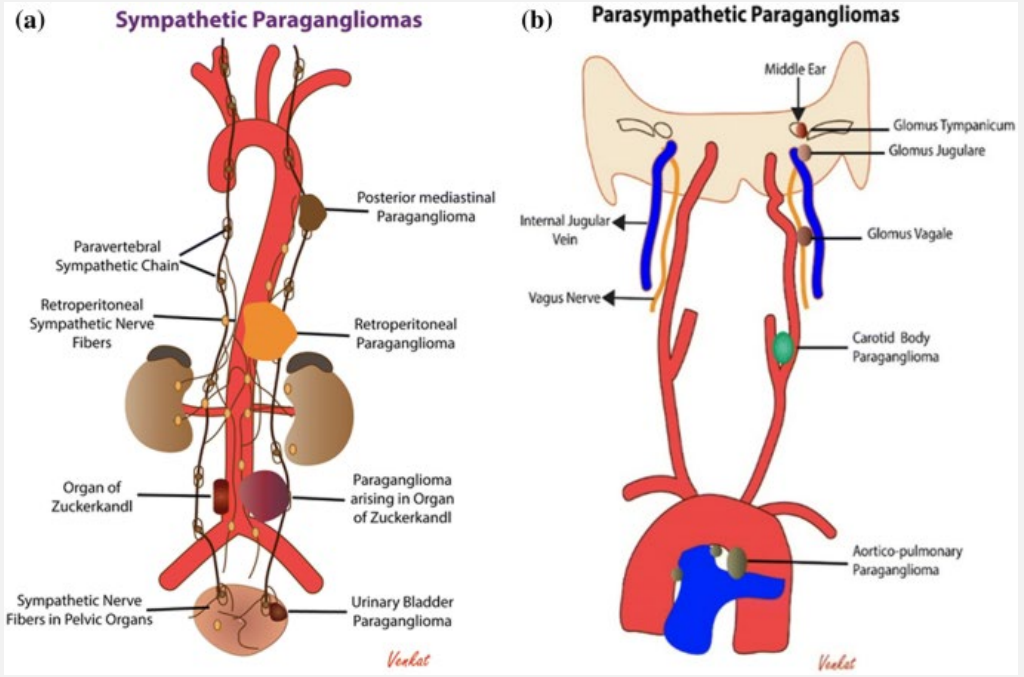
Omaha, NE

Omaha Regional PHEO PARA Patient Conference

August 12, 2023

# PHEOCHROMOCYTOMAS(PHEO) AND PARAGANGLIOMAS (PARA)

- Tumors of the autonomic nervous system: 2-8 million persons affected
  - Pheos (adrenal medulla), Paras (extra adrenal paraganglia)
- 40% arise in persons with a known germline genetic mutation
- Metastatic disease: 15-25% of all pheos and paras
  - 40% of metastatic pheos and paras have a known genetic mutation.
  - 80% lymph nodes, 71% bone, 50% lungs
  - Most are slow growing and 50-70% 5- year survival: chronic disease
  - Some tumors can behave aggressively




NANETS guidelines. Pancreas journal.2021;50(1)

# SYMPTOMS

- HTN
- Sweating
- Headaches
- Palpitations
- Orthostatic hypotension
- Anxiety
- High blood sugars
- Sense of doom
- vomiting

- **Clinical Feature Score**
- Pallor: 1
- Hyperhidrosis: 1
- Palpitations:1
- Tremor: 1
- Nausea: 1
- BMI < 25: 1
- Pulse ≥ 85: 1
- Obesity: -1
- Score of 3.8 or more has almost 6 fold probability of Para/Pheo

Not all people have "classic" symptoms
Some report "spells"

Nolting et al. Endocrine Reviews 2022;43(2)

# PRECIPITANTS OF "SPELLS" OR PARA/PHEO SYMPTOMS

Food containing Tyramine

Red Wine

Beer

Aged cheeses

Procedures

surgery, anesthesia, endoscopy

Severe stress

Elevated intraabdominal pressure

palpation, defecation, pregnancy

Medications:

- Glucocorticoids, metoclopramide
- Droperidol
- MAO inhibitors
- Tricyclic antidepressants
- Opiates (fentanyl, morphine)
- Naloxone
- Glucagon
- Some antibiotics
- Phentermine, sibutramine
- Chemotherapy
- Stimulants

Nolting et al. Endocrine Reviews 2022;43(2)

# GENETIC MUTATIONS

NANETS guidelines. Pancreasjournal.2021;50(1)

| Gene | Risk of Pheo/Para | Location | Risk of metastasis |
|---|---|---|---|
| NF1 | 1-13% | Pheo | 12% |
| VHL | 20% | Pheo | <5% |
| RET (MEN2) | 50% | Pheo | <5% |
| SDHA | 10% | Para, Pheo | 12% |
| SDHB | 25% | Para, HN, Pheo | 25-50% |
| SDHC | Low | HN, Thoracic | <5% |
| SDHD | 45% | HN, Para, Pheo | <5-8% |
| SDHAF2 | Low | HN | Low |
| TMEM127 | Low | Pheo, para less | <5% |
| MAX | Unknown | Pheo | unknown |
| FH | Low | Para | May be high |

# GENETIC SCREENING

- All patients with Pheo/Para (primary or metastatic) should have germline testing for mutations  associated with pheo/para
- Family should also be tested for germline mutation if there is a known mutation in the family
- Recommend having this done before surgery if possible
  - This may change extent of surgery or pre-operative workup and evaluation for metastasis

# DIAGNOSIS

- **All persons with Pheo/Para (or suspected) should have biochemical evaluation before surgery!!**
- Pre-operative biochemical evaluation:
  - Plasma-free or 24 hour hour urine metanephrines and normetanephrines
    - 2 fold increase above ULN
      - Intra adrenal: metanephrines
      - Extra-adrenal; normetanephrines
  - Do not recommend routine testing of catecholamines
  - Catecholamines can be helpful if evaluating for dopamine secretion (methoxytyramine is metabolite)
  - Chromogranin A; controversial, not routinely recommended

# THINGS TO AVOID PRIOR TO BIOCHEMICAL TESTING

Coffee

Tea

Bananas

Chocolate

Cocoa

Citrus fruits

Vanilla

Acute stress

Vigorous exercise

Caffeine

- Tylenol
- Levodopa, methyldopa
- Labetolol, carvedilol
- Tamsulosin
- Venlefaxine
- HCTZ
- Buspirone
- Lamotrigine
- Aribiprazole
- Stimulants (Ritalin, Adderall, Vivance)
- MAO inhibitors

Beware of false positive results

# CLONIDINE SUPPRESSION TEST

- For normetanephrine level 3-4 times ULN
- Can be helpful differentiating false positive tests from real elevations
- Other health conditions can also contribute to falsely elevated levels:
  - Obstructive sleep apnea
  - Psychological stress
  - Physical stress
  - Hypoxemia (low oxygen)
  - Chemotherapy
  - Radiotherapy

Pommer et al. JCEM;107(9)
Remde et al. Hypertension.2022;79(6)

# IMAGING

- Pre-operative imaging
  - Cross sectional imaging (CT or MRI) of the area where the tumor is located
  - Imaging for metastatic disease should be done in those who have concern for metastatic disease; cross sectional imaging with neck, chest, abd/pelvis CT or MRI
    - Functional imaging: not routinely done preoperatively or for post-op surveillance
      - I-123 MIBG (not as sensitive, but helpful if considering therapy with MIBG)
      - PET/CT: higher sensitivity for metastatic Para
        - Ga68-DOTATATE PET/CT: best sensitivity for metastatic Para (should be done if considering PRRT)
        - FDG PET/CT; better than I-123 MIBG, not as sensitive as DOTATATE

# PRE-OPERATIVE ALPHA BLOCKADE

- For Pheos and Paras that are secretory
- Treat with alpha blockade for at least 7-14 days to achieve adequate hormone blockage and bp control prior to surgery.
  - Alpha blockade (first choice)
    - Addition of beta blockers for tachycardia (only after adequate alpha block)
  - Calcium channel blockers:  can add to the above, but do not recommend monotherapy
  - Metyrosine:  blocks production of catecholamines,
    - Expensive and not widely available
- High salt diet and fluid expansion

**TABLE 5.** Medications Commonly Used for Hemodynamic Control in Patients With PPGL

| Class of Drug | Drug Name | Average Dosing | Special Issues | Common Adverse Effects |
|---|---|---|---|---|
| α-Blockers | | | | |
| Selective α1 blockers | Doxazosin | 2–8 mg given every 12–24 h | Less potent than nonselective α-blockers | Orthostatic hypotension, dizziness, tachycardia |
| | Prazosin | 2–5 mg given every 8 h | Less potent than nonselective α-blockers | Orthostatic hypotension, dizziness, tachycardia |
| | Terazosin | 4–8 mg given every 12–24 h | Less potent than nonselective α-blockers | Orthostatic hypotension, dizziness, tachycardia |
| Nonselective α-blocker | Phenoxybenzamine | 10–20 mg given every 8–12 h | Expensive, supply limited at times; irreversible binding to α receptors | Orthostatic hypotension, nasal congestion, tachycardia |
| β-Blockers | | | | |
| Selective β1-blocker | Metoprolol tartrate | 25–50 mg given every 12 h | Aim for heart rate <90/min | Fatigue, dizziness, asthma exacerbation |
| | Atenolol | 25–50 mg given once or twice daily | Aim for heart rate <90/min | Fatigue, dizziness, asthma exacerbation |
| Nonselective β-blocker | Propranolol | 20–40 mg given every 8–12 h | Aim for heart rate <90/min | Fatigue, dizziness, asthma exacerbation |
| α-Blockers and β-blockers | | | | |
| | Labetalol | 200–2400 mg daily | Used only after the α-blocker as labetalol is a more potent β than α antagonist | Fatigue, dizziness |
| | Carvedilol | 6.25–50 mg given every 12 h | Used only after the α-blocker as carvedilol is a more potent β than α antagonist | Fatigue, dizziness |
| Calcium channel blockers | | | | |
| | Amlodipine | 5–10 mg daily | Nondihydropyridine calcium channel blocker preferred | Edema, headache |
| | Nifedipine | 30–60 mg given every 12 h | Nondihydropyridine calcium channel blocker preferred | Edema, headache |
| Tyrosine hydroxylase inhibito | | | | |
| | Metyrosine | 250–500 mg titrated up to every 6 h | It inhibits the regulatory enzyme of the catecholamine synthesis; not always available, expensive | Severe fatigue, extrapyramidal neurologic adverse effects, nausea, diarrhea, anxiety |

# PREDICTORS OF AGGRESSIVENESS

- Large tumor size:  (> 5 cm adrenal), (> 4 cm extra adrenal)
- Gross vessel invasion
- SDHB mutations
- After resection:
  - Tumor with lymph nodes involved
  - Elevated biochemical markers (metanephrines/normets) 8 weeks post op
  - High Ki-67 > 2-5%

NANETS guidelines. Pancreasjournal.2021;50(1)

# STAGING: AJCC 8TH ED

NO LONGER "BENIGN OR MALIGNANT"
"NON-METASTATIC" OR "METASTATIC"

ALL PERSONS SHOULD HAVE STAGING PERFORMED

| Tumor | N (regional LN) | Metastasis | Stage |
|---|---|---|---|
| T1 | N0 | M0 | I |
| T2 | N0 | M0 | II |
| T1 | N1 | M0 | III |
| T2 | N1 | M0 | III |
| T3 | N0 | M0 | III |
| T3 | N1 | M0 | III |
| Any T | Any N | M1 | IV |

T1= pheo < 5 cm,
T2= ≥ 5 cm
T3= invasion of surrounding tissues

M1= distant mets
M1a= bones
M1b=lymph nodes/liver/lungs
M1c=bones + other sites

# POST OPERATIVE SURVEILLANCE

- Yearly plasma metanephrines/normets for secreting tumors
- Cross sectional imaging of tumor site initially 3-6 months post-operatively, then yearly for those high risk of metastatic disease
  - If genetic mutation: neck, chest, abd/pelvis imaging yearly initially and if negative every 3 years.
  - If metastatic disease; every 3-6 months with cross sectional imaging
  - If metastatic disease and considering radiolabelled therapy: PET/CT or MIBG

# RECURRENT OR METASTATIC DISEASE

- Screening with blood/urine metaneprhines/normets and imaging will assist with detection of recurrent or metastatic disease.
- If surgically resectable, then resect AFTER alpha blockade (Dr. Fingeret)
- If un-resectable, then consider additional treatment options
  - Medical options (Dr. Dillon)
  - Radiolabelled treatments (Dr. Dillon)
  - Clinical Trials (Dr. Pacak)

# WHAT IS RECOMMENDED IF YOU FIND OUT YOU HAVE A GENETIC MUTATION PUTTING YOU AT HIGHER RISK FOR PHEO/PARA?

- RET: screen for pheo/para with plasma metanephrines/normets, medullary thyroid carcinoma and hyperparathyroidism
- SDHx mutations:
  - Plasma-free metanephrines/normets every year as an adult
  - MRI every 3 years (whole body) vs MRI neck and abd + CT chest
  - PET/CT could be done as initial screening but is not not routinely recommended in asymptomatic mutation + persons with no tumors

Amar et al. Nature Reviews. 2021; 17
Hansen et al. BMJ; 2022

# QUESTIONS?

- Thank you!