1/ 🎙️Hello #MedTwitter

This month’s @ASPNeph Renal Imaging Webinar was all about #Pheochromocytoma!

Here are a few “pheo facts” I learned! #tweetorial #nephtwitter

Let’s start with a poll.

Which of the following is true about pheochromocytoma (PCC)?
PCC & Paraganglioma (PGL) are catecholamine secreting tumors arising from chromaffin cells.

PCC ➡️ Adrenal medulla = 80-85%
PGL ➡️ Extra-adrenal = 10-15% ➡️ sympathetic chain (abdo/chest/pelvis) or parasymp chain (head&neck)
Many will recall the “Rule of 10s”
10% Malignant
10% Family history
10% Bilateral
10% Extra-adrenal

But..
- This rule does not hold true for children
- In particular, inherited PCC/PGL more likely in children
- Up to 80% in some studies! (PMID:24169644)

4/ Which Syndromes are associated with PGLs/PCCs?
Von Hippel Lindau: PCC (often B/L) or PGL in ~10-20%. Noradrenergic phenotype. Gene: VHL TSG

MEN2: PCC in ~50%. Adrenergic phenotype. Gene: RET

NF1: common ~2-3%. Usually solitary PCC. Gene: NF1

All =AD inheritance

Source:

http://UptoDate.com
6/ Many other susceptibility genes identified

Genetic mutations can be divided into 2 groups:
- Genes encoding proteins
- Hypoxia inducible factors: VHL, SDH, EGLN1 & HIF2A
- Kinase Signalling pathway: RET, NF1, TMEM127

Genetic Testing is recommended in all children

7/ Approximately how common is the classic triad of episodic headache, sweating and palpitations in children?
8/ The classic triad has been reported in up to 54% of children (PMID: 24825268)

Average age ~ 11-13 years
M&gt;F 2:1

Other symptoms:
anxiety weight visual change
polydipsia/uria glucose tremor flushing
abdo pain diarrhoea pallor syncope

9/ Hypertension is common (60-90%)
Sustained &gt; paroxysmal in children
BP can be normal
Look for abnormal ABPM eg. “non-dipping”

Orthostatic Hypotension can be a presenting feature (epinephrine secreting tumours)

(PMID: 30603807)
10/ Let’s Review catecholamine production & metabolism!

Catecholamines are produced by metabolism of Tyrosine ➔ DOPA ➔ Dopamine ➔ Norepinephrine ➔ Epinephrine

⚡ Metanephrines are the o-methylated products of catecholamine metabolism ⚡

(PMID: 30603807)

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Fig. 1 Catecholamine metabolism and genetic mutations associated with hormonally active tumors. Combining information from figures in Lenders et al. [2] and Fishbein et al. [15]
11/ 1st line of invx is biochemical testing

⚡ Catecholamines or metanephrines can be tested
⚡ Plasma metanephrines more sens/specific than urine
⚡ Suspect false 🙅‍♂️ if level <3-4 x normal

⏰ Patient should be supine x 30mins for plasma sample
😢 Use age appropriate cut-offs

12/ Which of the following medications can cause elevation of catecholamines?

13/ All the above

⚡ Sympathomimetics, SSRIs, MAO inhibitors, α/β blockers ➡️ false ➡️ catecholamines
⚡ Acetaminophen interferes w/ liquid chromatography
⚡ Stop medications ~2 wks prior to testing
⚡ If not, ➡️ Clonidine suppression test

(PMID: 21615192, 28752085, 21651412)
TABLE 4  | Factors associated with false positive and false negative testing of metanephrines.

**False positives**

<table>
<thead>
<tr>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications (3)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td>Beta blockers</td>
</tr>
<tr>
<td>Mood stabilizers: tricyclic antidepressant, buspirone</td>
</tr>
<tr>
<td>Sympathomimetics: amphetamine, ephedrine</td>
</tr>
<tr>
<td>Stimulants: caffeine, nicotine</td>
</tr>
<tr>
<td>Dopaminergic agents: levodopa, alpha-methyldopa</td>
</tr>
<tr>
<td>Acetaminophen</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Increase in plasma metanephrines with age (51)</td>
</tr>
<tr>
<td>Posture</td>
</tr>
<tr>
<td>Increase in plasma metanephrines in seated versus supine position (52, 53)</td>
</tr>
<tr>
<td>Exercise (52)</td>
</tr>
<tr>
<td>High catecholamine diet (54)</td>
</tr>
<tr>
<td>Hypertension (3)</td>
</tr>
<tr>
<td>Obstructive sleep apnea (53, 55)</td>
</tr>
<tr>
<td>Stroke (3)</td>
</tr>
<tr>
<td>Renal impairment (56)</td>
</tr>
</tbody>
</table>

**False negatives**

<table>
<thead>
<tr>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small tumors, usually &lt;2 cm in size in normotensive patients being screened initially or for recurrence</td>
</tr>
<tr>
<td>Dopamine-secreting tumors</td>
</tr>
</tbody>
</table>
**Figure 1**
Mechanisms of Pharmacologic Interference with Catecholamines and Metanephrines

Sympathomimetic agents such as ephedrine, amphetamine, caffeine, and nicotine increase the release of norepinephrine and epinephrine. Monoamine oxidase (MAO) inhibitors block the conversion of norepinephrine and epinephrine to dihydroxyphenylglycol (DHPG), leading to increased concentrations and availability of these two catecholamines. Drugs that inhibit norepinephrine and epinephrine reuptake, such as serotonin–norepinephrine reuptake inhibitors (e.g., venlafaxine), "selective" serotonin-reuptake inhibitors, and tricyclic antidepressants, lead to increased concentrations of norepinephrine and epinephrine in the synaptic clefts. The α-adrenergic-receptor blockers and β-adrenergic-receptor blockers reduce the effects of catecholamines on end organs such as the brain, heart, gastrointestinal tract, and others. DOPA denotes dihydroxyphenylalanine.
14/ Biochemical results can help classify the tumour:
- Adrenergic: E, NE, M, NM, VMA
- Noradrenergic: NE, NM, VMA
- Dopaminergic: Dopamine, HVA

15/ Imaging localise tumour & identify mets CT & MRI both good sens & specificity

- Features can include:
  - attenuation on non-con CT (most >20 HU)
  - vascularity, cystic or hemorrhagic change
  - Delayed contrast washout
  - T2 signal on MRI

Source:

http://uptodate.com
16/ Functional imaging can be used to:
- Localise tumour when CT/MRI negative
- Identify metastatic/multifocal disease
- Follow-up screening

Functional imaging may include integrated PET CT/MRI or scintigraphy

Let’s review some options:

17/ MIBG Scintigraphy:
- Iobenguane I-123 is a compound similar to NE
- Uptake at adrenergic tissue
- Uptake in normal adrenals can by asymmetrical
- Correlate with CT/MRI

PMID: 21803186
**Figure 1**

Whole body (left) and anterior reprojected images (right) with $^{123}$I-MIBG of a patient with PHEO; multiple metastatic lesions are seen.
18/ FDG PET:
- FDG is a glucose analogue
- Useful in tumours with ↑ glycolytic activity

Ga68 DOTATATE PET:
- Somatostatin analogue
- Good uptake in well-differentiated tumours
  - ↑ Sensitivity &amp; ↑ Resolution
  - ↓ Radiation

PMID: 19372492
19/ This helpful diagram from a comprehensive review or PCC/PGL (PMID:30603807) summarises an approach to diagnostic evaluation:
Surgical removal of a PCC/PGL can trigger a life threatening catecholamine storm.

This can cause:
- Hypertensive Crisis
- Arrhythmias
- Myocardial infarction
- Stroke

Also post-operatively a drop in catecholamines can lead to \( \downarrow \) BP
21/ Aim of medical management is to prevent fluctuations in BP & post op \( \downarrow \) BP

Always THINK \( \textbf{A} \) before \( \textbf{B} \)
Start with alpha blockers before beta blockers!

\( \text{bolt}\)Initial use of beta blockers \( \rightarrow \) unopposed alpha action \( \rightarrow \) catecholamine storm \( \text{bolt}\)

22/ There are no internationally approved protocols for management of PCC/PGLs

The table below summarises a suggested approach (PMID:30603807)

\( \text{bolt}\)Metyrosine = tyrosine hydroxylase inhibitor \( \rightarrow \) catecholamine synthesis +/- alpha blockers can \( \downarrow \) BP lability peri-op
23/ Take home points:
⚡ PCC/PGL are rare
⚡ Only ~50% have classic symptom triad
⚡ Genetics testing for all children
⚡ Biochemistry ➔ CT/MRI ➔ Functional imaging
⚡ Remember A before B to avoid a catecholamine storm!!

Thanks #ASPNeph #FellowFOAMgroup
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