Budapest Nephrology School
Secondary Hypertension

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August 2010
Objectives

- Define Secondary Hypertension
- Incidence of secondary HTN
- Primary Hyperaldosteronism
- Pheochromocytoma
- Renal Artery Stenosis
- Determine who to work up for secondary HTN
- Best Screening tests for secondary hypertension
Secondary Hypertension

- 90% of patients have essential or primary hypertension.
- These patients usually have positive family history of hypertension.
- **Secondary hypertension** is when an underlying physiological or anatomical cause of hypertension is found.
More common causes of Secondary Hypertension

- Renal Disease
- Renal Artery Stenosis
- Primary Hyperaldosteronism
- Pheochromocytoma
Primary Hyperaldosteronism

• Found to be increasingly common in patients with severe or resistant HTN

• May account for 5% of all hypertensives

• Reported in different series to be present in up to 38% of patients with resistant HTN
Primary Hyperaldosteronism

- Autonomous secretion of aldosterone from the adrenal cortex
- Elevated aldosterone levels result in suppression of renin levels
- Increased aldosterone results in sodium retention, HTN, loss of potassium in the urine, hypokalemia, metabolic alkalosis
Primary Hyperaldosteronism

- Conn’s Syndrome - Unilateral adrenal adenoma
- Bilateral Adrenal Hyperplasia
- Important to distinguish between these 2 causes as the treatment of the conditions differs
Diagnose Hyperaldosteronism

- Make a biochemical diagnosis before imaging
- Ratio of aldosterone: renin > 30:1
- Plasma aldosterone level > 15
- 24 hr urine aldosterone elevated
- Low or normal K levels
- Metabolic alkalosis

- If biochemical evidence, need imaging study to assess adenoma vs bilateral hyperplasia (CT abdomen)
Conn’s Syndrome

- Unilateral adrenal adenoma
  - Specific appearance on CT scan due to increased fat content (<10 Hounsfield units)

- Treat surgically in most patients
  - Laparoscopic adrenalectomy
  - Adrenal Vein Sampling prior to surgery to confirm lateralization

- Can treat medically in mild cases, elderly or poor surgical candidates
Adrenal Adenoma
Bilateral Adrenal Hyperplasia

- CT abdomen: Bilateral Thickening or nodularity of Adrenal limbs
- Always treat medically
- No role for surgery
- Use aldosterone inhibiting drug: Aldactone, Eplerenone, Amiloride
Primary Aldosteronism

- Glucocorticoid remedial hypertension
- Liddle's Syndrome

Aldosterone

Mineralocorticoid Receptor

Cortisol

11-βHSD2

Cortisone

Activated mutant Mineralocorticoid Receptor

HRE

Apparent Mineralocorticoid Excess

Epithelial Sodium Channel

Na+

K+

ACTH

Chimeric ACTH-Aldosterone Synthase gene
Primary Hyperaldosteronism

- Spironolactone - need to use high doses usually in the range of 50-100mg twice daily
  - Is NOT tolerated by male patients

- Eplerenone - less potent but definitely less gynecomastia and less hyperkalemia

- Amiloride - well tolerated, occasionally GI side effects can use up to 10 mg twice daily, problem amiloride only comes in 5 mg tablets
Lateralization index (LI) = ipsilateral A/C ratio [ng/dL/mcg/dL] over contralateral A/C ratio: 76/2.5 = 31

Selectivity index (SI) = ratio of cortisol level in each adrenal vein compared with IVC.
Right 1090/23 = 47
Left 680/23 = 30
# AVS Results

<table>
<thead>
<tr>
<th></th>
<th>Aldo</th>
<th>Cortisol</th>
<th>Ratio</th>
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<tr>
<td>R adrenal</td>
<td>2590</td>
<td>1090</td>
<td>2.5</td>
</tr>
<tr>
<td>L adrenal</td>
<td>52</td>
<td>100</td>
<td>76</td>
</tr>
<tr>
<td>IVC</td>
<td>110</td>
<td>23</td>
<td>4.7</td>
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</table>
Primary Hyperaldosteronism

• More common than previously thought

• Worthwhile screening patients particularly with severe or resistant hypertension

• Potential cure of HTN
Pheochromocytoma

• Rare cause of hypertension

• Approximately 800 new cases diagnosed annually in the United States

• Penn: 30-40 new cases per year and 70-100 patients in follow up per year
Autonomic nervous system

- Innervates vascular and visceral smooth muscle, exocrine and endocrine glands, and parenchymal glands throughout the organs

- Two divisions
  - Sympathetic chain, includes the adrenal medulla
  - Parasympathetic ganglia
Tumors of the Autonomic Nervous System

• Adrenal medulla
  – Pheochromocytoma

• Sympathetic chain
  – Sympathetic paraganglioma – usually located retroperitoneal, but can be found in abdomen or thorax, usually secrete catecholamines
    • Usually termed extra adrenal pheochromocytoma

• Parasympathetic ganglia
  – Parasympathetic paraganglioma usually in the head and neck region, generally biochemically silent
    • Glomus tumors, chemodectomas, carotid body tumors
Sites of Paraganglionomas
Pheochromocytoma

• Chromaffin cells are derived from the neural crest which function as post-synaptic nerve cells

• Unregulated growth of chromaffin cells results in the development of pheochromocytomas which can occur in the adrenal gland or in an extra-adrenal location

• Norepinephrine (NE) is converted to epinephrine (E) in the adrenal medulla

• Pheo - Increased catecholamine secretion

• NE is predominantly excreted and causes intense stimulation of alpha receptors
Pheochromocytoma

- Alpha receptors are stimulated resulting in hypertension, tachycardia, palpitations and headaches
- Not all patients have these classic symptoms
- BP can be labile
- Rare cause of hypertension
Pheochromocytoma

- Previously “10%” tumor
- 90% of lesions are found in the adrenal gland
- 10% extra-adrenal (paraganglionomas)
- 10% bilateral
- (10%) 20-30% malignant
- 30-40% genetic in origin
Metabolic Pathway

FIG. 1. Catecholamine biosynthesis.
Metabolic Pathway

NOREPINEPHRINE

MAO

COMT

OH
CH₂CH₂NH₂

OH
CH₂CH₂NHCH₃

EPINEPHRINE

AD
COMT

CH₃O
CH₂OH

OH
CH₂CHO

3-METHOXY-4-HYDROXY-PHENYLGLYCOL (MHPG)

AO

CH₃O
CH₂COOH

OH
CHCOOH

DIHYDROXYMandelic Acid

COMT

AO

CH₃O
CH₂COOH

3-METHOXY-4-HYDROXYMandelic Acid
(VANILLYLMANDelic Acid, VMA)

MAO

CH₃O
CH₂NH₂

OH
CH₂NHCH₃

NORMETANEPHRINE

METANEPHRINE
Plasma Metanephrines

- Newest measure, most sensitive and specific

- Initially recommended that levels are drawn after 20 minute rest and in fasting state

- No acetaminophen for 5 days

- Newer data shows that levels can be done without rest period but need to be interpreted with higher upper limit of normal

- If borderline values can repeat supine after rest or order 24 hour urine
24 hour urine for catecholamines

• Previously most reliable test

• Order metanephrines, catecholamines, VMA

• Total urine metanephrines - most useful, not affected by drugs or food

• False positive with certain drugs: labetalol, clonidine and buspar

• Increase in VMA alone due to ingestion of vanilla products
How to screen for pheo in dialysis patients

• Cannot measure 24 hr urines
• Plasma catecholamines have been shown to consistently elevated in HD patients but never more than 3-fold (Mayo)
• Plasma catecholamine levels are inversely elevated with decreasing renal function
• Study from NIH showed plasma free metanephrines are relatively independent of renal function and are, therefore, more suitable for diagnosis of pheochromocytoma among patients with renal failure or in dialysis patients
Diagnosis of Pheochromocytoma

• Plasma metanephrines (BEST SCREENING TEST)

• 24 hour urine for catecholamines, metanephrines, VMA

• Values are usually 3-4 x greater than normal

• If borderline values and strong clinical suspicion, can pursue further testing
Other Screening Tests

- **Plasma Catecholamines** - less reliable, often abnormal, do not order as a screening test

- **Clonidine suppression test** - difficult, rarely done

- **Chromogranin A** - co-stored and co-secreted with catecholamines, levels increased in 80% of pts with pheo
  - Decreased utility as it has a low specificity
  - Useful to follow patients with metastatic disease
## Biochemical Testing

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<th>Spontaneous</th>
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<tr>
<td></td>
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<td>sensitivity/specifcity</td>
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<tr>
<td>Plasma Met</td>
<td>97/96</td>
<td>99/82</td>
</tr>
<tr>
<td>Plasma Cat</td>
<td>69/89</td>
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<tr>
<td>Urine Met</td>
<td>96/82</td>
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<tr>
<td>Urine Cat</td>
<td>79/96</td>
<td>91/75</td>
</tr>
<tr>
<td>Total Urine Met</td>
<td>60/97</td>
<td>88/89</td>
</tr>
<tr>
<td>VMA</td>
<td>46/99</td>
<td>77/86</td>
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Pheochromocytoma

• If biochemical tests are positive, patient need radiographic imaging to localize the tumor

• CT/MRI abdomen (adrenal glands)
Once diagnosis is confirmed, how to proceed

• Treatment of choice is laparoscopic adrenalectomy for adrenal tumors

• Adrenal sparing surgery if possible if bilateral tumors

• Patients need to be well prepared prior to surgery as major morbidity is associated with removal of these tumors
Catecholamine Biosynthesis

FIG. 1. Catecholamine biosynthesis.
Pre-operative preparation

- Peripheral alpha blocker: phenoxybenzamine 10-60 mg

- Side Effects: severe postural hypotension, tachycardia, nasal congestion, GI side effects

- Begin 2-3 weeks prior to surgery or as soon as diagnosis is confirmed
Pre-operative preparation

• Never use beta-blocker until fully alpha blocked as can get unopposed stimulation of alpha receptors

• Once alpha-blocked, if tachycardic can add beta blocker
Pre-operative preparation

• Alpha-methyl tyrosine (demser) prevents conversion of catecholamines to active form

• Blocks Tyrosine Hydroxylase preventing conversion of tyrosine to L-dopa

• Begin 2 weeks prior to surgery, titrate dose

• Side effects: extra pyramidal neurological problems, severe lethargy, GI side effects
During Surgery

• Use IV phentolamine (alpha blocker) to maintain BP and prevent BP surges

• Typical response is to see BP surges when tumor is manipulated and severe hypotension once tumor is removed

• Post-op usually require alpha agonist to support BP (norepinephrine) for first 48 hours
Post-op follow up

• Repeat 24 hr urine and/or plasma metanephrines at 6 weeks and every 6 - 12 months after

• There is a possibility of recurrence

• Recurrence more likely with malignant tumors and extra-adrenal tumors
Benign vs Malignant

- 80% - benign, 20-30% - malignant
- Very difficult to distinguish benign vs. malignant
- Histologically can appear identical
- Extra-adrenal tumors, multiple sites more likely to be malignant
- Macroscopic appearance of tumor may be helpful - tumor encapsulated, local invasion or distant metastases
- Most tumors are indolent and slow growing
- Certain tumors associated with SDHB mutation can be highly malignant and very aggressive
Histology

- **Pass Score** (pheochromocytoma of the adrenal gland scoring scale): scoring system (maximum score is 20) is based on the presence of 12 different histologic parameters, including tumor necrosis, mitotic rate, tumor cell spindling, and the presence of large cell nests

  - >6 high malignant potential
  - 4-6 need close follow up
  - <4 low malignant potential
Imaging studies for metastatic disease

- Octreotide scan - not often used
- MIBG 131
- MIBG 123
- FDG PET scan (SDHB)
- FDA PET scan
MIBG Scan

- Nuclear medicine scan which shows increased area of radio-active tracer in area of excess catecholamine secretion

- MIBG: resembles NE and is taken up by adrenergic tissue

- I-131: more commonly done, need to pre-treat with lugols iodine to prevent thyroid crisis, less sensitive than I-123, used in treatment of pheo (MIBG therapy)

- I-123: very difficult to obtain, now available at Penn, better imaging and more sensitive for pheo, need minimal iodine prep
Treatment Options For Malignant Pheo

- Not well defined
- Watch and wait
- Chemo - several regimens have been tried with minimal response in most cases
- Radiation reserved usually for bone metastases
- Radio-active MIBG - best option
- Surgery - debulking
- ?VEGF inhibitors
MIBG Treatment

• High dose MIBG used in the past but increased toxicity
• Currently at PENN using low dose MIBG of 2mCi/kg every 3-4 months
• Maximum dose of 1000 mCi/kg
• Monitor CBC weekly for 8 weeks
• Well tolerated and done as an outpatient procedure
• New trial evaluating different form of delivery of MIBG (Azedra) with higher dose MIBG
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Chr</th>
<th>Major component</th>
<th>Other manifestations</th>
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<tbody>
<tr>
<td>PGL 1*</td>
<td>SDHD</td>
<td>11q23</td>
<td>PHEO or PGL</td>
<td>-------</td>
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<td>11q13</td>
<td>PGL</td>
<td>-------</td>
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<td>PGL 3</td>
<td>SDHC</td>
<td>1q21-23</td>
<td>PGL</td>
<td>-------</td>
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<tr>
<td>PGL 4</td>
<td>SDHB</td>
<td>1p36</td>
<td>PGL</td>
<td>Renal clear cell cancer</td>
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<td>PHEO</td>
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<td>PGL</td>
<td>Gastric stromal sarcoma</td>
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<td>VHL</td>
<td>3p25-26</td>
<td>PHEO</td>
<td>Hemangioblastomas (brain, spine, retina) Renal clear cell cancer Pheochromocytoma</td>
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<tr>
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<td>RET</td>
<td>10q11.2</td>
<td>PHEO</td>
<td>Medullary thyroid carcinoma Parathyroid hyperplasia</td>
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<tr>
<td>NF 1</td>
<td>GNDF</td>
<td>17q11</td>
<td>PHEO</td>
<td>Neurofibromas, café-au-lait spots Lisch nodules Plexiform neurofibromas Malignant peripheral nerve sheath tumors</td>
</tr>
</tbody>
</table>
Carotid body tumors

- In 1987 reported that people living in the Andes had an increased incidence of carotid body tumors (1987)

- High altitude causes chronic hypoxia

- Report from 1970s showing that patients in the Andes with carotid body tumors had increased succinate levels

- In 2000 linkage studies from families in the Netherlands in with apparent pheo/PGL syndromes showed mutations in the SDH complex
Familial pheo/PGL

- Succinate dehydrogenase (SDH) catalyzes the conversion of succinate to fumarate in the Krebs cycle

- Succinate dehydrogenase (SDH) or mitochondrial complex II is comprised by four subunits (A–D) in the inner mitochondrial membrane

- SDH subunits are encoded by autosomal genes
SDH complex
• Germline heterozygous mutations in SDHD were found to cause familial and apparently sporadic pheochromocytoma/PGL (2000)

• Subsequently, germline heterozygous mutations in SDHB and SDHC were also found in heritable pheo and PGL

• Recent mutations identified in SDHA

• SDHB mutations have been associated with malignancy, decreased survival and renal cell carcinoma
# What is the Difference

## SDHB/C/D PGL

<table>
<thead>
<tr>
<th>Familial PGL Syndrome</th>
<th>PGL1</th>
<th>PGL3</th>
<th>PGL4</th>
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<tbody>
<tr>
<td>SDH subunit</td>
<td>SDHD</td>
<td>SDHC</td>
<td>SDHB</td>
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<tr>
<td>Mutation in gene locus</td>
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<td>1q21</td>
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## What is the Difference SDHB/C/D PGL

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<th></th>
<th>SDHD</th>
<th>SDHC</th>
<th>SDHB</th>
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</thead>
<tbody>
<tr>
<td>Chest/abdomen/pelvis</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Adrenal</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Extra-adrenal</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>multifocal</td>
<td>+</td>
<td>_</td>
<td>++</td>
</tr>
<tr>
<td>malignant</td>
<td>rare</td>
<td>_</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Head/Neck</strong></td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>multifocal</td>
<td>+++</td>
<td>_</td>
<td>+</td>
</tr>
<tr>
<td>malignant</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
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</table>
Using von-Hippel Lindau as a model to connect HIF and VEGF

Control of Hypoxia-Inducible Factor (HIF) by the Gene Product of the von Hippel–Lindau Gene (pVHL).

HIF is a heterodimer consisting of an α subunit and a β subunit. In the absence of oxygen, HIF-α is hydroxylated on one of two proline residues. The pVHL binds to hydroxylated HIF-α and directs the attachment of a polyubiquitin chain, which targets HIF-α for destruction by a multiprotein complex called the proteasome. Under hypoxic conditions, or in the absence of pVHL, HIF-α accumulates and activates the transcription of hypoxia-inducible genes. VEGF denotes vascular endothelial growth factor, PDGF-β platelet-derived growth factor β, TGF-α transforming growth factor α, and EPO erythropoietin.
Consider genetic testing in sporadic pheochromocytoma if age at diagnosis < 50 for mutations in

\[ VHL, RET, SDHD, SDHB \]

using the patient’s findings and table below as a guide

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Average age of diagnosis</th>
<th>Adrenal disease</th>
<th>Multifocal adrenal disease</th>
<th>Extra-adrenal disease</th>
<th>Predominant biochemical profile</th>
<th>Mutation frequency</th>
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<tr>
<td>MEN 2</td>
<td>RET</td>
<td>35-40</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>Metanephrine</td>
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<tr>
<td>VHL</td>
<td>VHL</td>
<td>20-30</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>Normetanephrine</td>
<td>high</td>
</tr>
<tr>
<td>SDHB</td>
<td>SDHB</td>
<td>20-30</td>
<td>+</td>
<td>-</td>
<td>++</td>
<td>Unknown</td>
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<tr>
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<td>SDHD</td>
<td>20-30</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>Unknown</td>
<td>medium</td>
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</table>
Genetic Testing

• SDHB and SDHD mutations are increasingly being detected

• Autosomal dominant mutations

• Affected family members require annual screening

• Screening guidelines controversial

• What age to start screening (? age 5)
Pheo/PGL

- The diagnosis and management of both adrenal and extra-adrenal pheos remain a diagnostic challenge
- Plasma metanephrines best screening test
- Levels greater than 4X normal definite pheo
- Refer all patients for genetic testing
- SDHB/SDHD mutations increasingly common
- Future challenges remain in treatment for metastatic disease and predicting who will have a poor outcome
Renal Artery Stenosis

• FMD: young females
• FMD: CT angiogram best screening
• FMD: can be missed with MRA

• FMD: can be bilateral, has excellent results with angioplasty, usually does not recur and does not need stenting
FIBROMUSCULAR DYSPLASIA: RENAL ARTERIOGRAM
Renovascular Hypertension

• Prevalence: 1-2% hypertensives
• Mechanism: Excessive renin secretion with increased Angiotensin II
• Presentation: Older patients, history of atherosclerotic disease, e.g. CAD, SMOKER
• Diagnosis:
  – Screening Test –MRA or CT angiogram [NSF!]
  – Confirmation: Angiogram-Radiocontrast or CO₂
• Management:
  – Antihypertensive including ACE or ARB
  – Angioplasty and Stent
RAS

- Dilemma as which test to use when screening for atherosclerotic RAS - this type of patient usually has DM and CKD so want to avoid iodinated IV contrast and Gadolinium

- Doppler studies very operator dependent and may be unreliable

- Angiography is the gold standard
Managing RVD

• Unilateral RVD – angioplasty and medical therapy are similar in control
• Bilateral RVD – usually will require more medication if managed medically; ischemic nephropathy may prompt angioplasty/surgery
• There is no “standard” antihypertensive regimen
• There is no standard of care
Sleep Apnea

• Worthwhile getting sleep study in resistant HTN as if diagnosed with sleep apnea often see improvement in BP control with use of CPAP
Who to work up for secondary HTN

- All young patients (<30yrs)
- New onset hypertension in older patients >70 years
- Sudden worsening of previously well controlled hypertension
- Strong suspicion for secondary HTN
- Negative family history for HTN
- Unusually severe HTN
Who to work up for Secondary HTN

- Unprovoked hypokalemia
- Triad of symptoms: headache, sweating and palpitations
- Epigastric bruit (RAS)
- Different BP measurements in the arms and legs or radiofemoral pulse delay
- Drug resistant hypertension
Initial Evaluation for Secondary HTN

- Plasma Renin
- Plasma aldosterone
- Plasma metanephrines
- CT angiogram / MRA
- Sleep study
Conclusion

• Secondary Hypertension accounts for 10% of hypertension

• Need to decide which patients are worthwhile to evaluate for secondary hypertension

• If diagnosis is confirmed, may be potentially curative form of HTN especially in a young patient