2 year-old Female with Hypertension
Chief Complaint

- 2 year and 6 month old female presented to the ER with 2 weeks of polydipsia and polyuria and 1 day of intractable vomiting.
- Following sedation for head CT on HD #2, she developed acute, malignant hypertension (200’s/140’s).
History of Present Illness

- 6 months PTA: Weight loss (~ 5 lb)
- 2 weeks PTA: Polyuria (20 diapers/day), polydipsia
- 1 day PTA: Intractable emesis (non-bloody, +green-tinged)
- On admission: Very fussy, but consolable. Generally sleepy and not as playful.

- Pertinent Negatives:
  - No sick contacts, no fever, no URI symptoms, no diarrhea.
Admission Plan:

- Rehydration
- Evaluation for emesis:
  - Abdominal US: normal
  - Infectious work-up: pending
- Evaluation for weight loss, polydipsia, polyuria
  - Glucose 92 mg/dL, insulin < 2 mIU/mL, c-peptide 0.31 pmol/mL, HbA1c 5%
  - GAD 65 (-), Anti-insulin AB (-), Znt8 (-), IA2 (-)
  - Na 142, spec grav 1.012, serum osm 275, urine osm 345
- Overnight developed AMS -> sedated with Propofol for following evaluation:
  - Head CT: enlarged ventricles
  - Brain MRI w/o contrast: above + parenchymal lesions
  - LP: CSF w/ high protein (1310), low wbc (6)
Hospital Day #2

- Developed elevated BP to > 150’s/130’s.
  - Hydralazine x 3
  - Started Nicardipine drip -> transferred to PICU
  - Added Clonidine, Labetalol, Losartan, and Lasix

- With regards to BP:
  - No history of HTN in the past
  - No history of kidney or cardiac disease.
  - Mother with HTN (presumed essential HTN, dx in 30’s)
Review of Systems

- General: + weight loss, +decreased appetite. No fever, fatigue.
- HEENT: No congestion or rhinorrhea. No visual disturbance.
- Resp: No SOB, no cough.
- CV: +HTN. No leg swelling.
- GI: +nausea, +vomiting x 1 day. +constipation. No abdominal pain or diarrhea.
- GU: +polyuria, +polydipsia. No hematuria.
- MSK: No arthralgias.
- Heme: No easy bleeding or bruising.
- Neuro: + AMS. +hearing loss. +increased reflexes
- Skin: + rash.
Past Medical History

- **Birth History**
  - 35-wk premature baby
  - 10-day NICU stay for feeding intolerance

- **Past Medical History**
  - Gastroesophageal reflux
  - Iron deficiency anemia
  - Normal gross and fine motor development
  - ? Speech delay – only says mama + few nonsensical words

- **Past Surgical History:**
  - None

- **Medications:**
  - None

- **Family History:**
  - HTN (mother)
  - Asthma (mother)
  - Type 1 DM (maternal aunt)

- **Social History:**
  - Lives with mother.
Physical Exam

- Tm 37.8C, P 121-200, BP 67-209/33-147, R 15-38. Wt 12 kg (23%), Ht 90 cm (39%), BMI 14.9 (17%).
- General: On admission was distressed but consolable.
- HENT: atraumatic head, no dysmorphic features, PERRL, anicteric sclera, normal TM, no tears despite crying. dry mm. oropharynx clear. dentition normal.
- Cardiac: tachycardic, no murmur. 2+ radial pulse. No edema. Cap refill 3-5 s.
- Resp: CTAB, normal effort.
- Abdomen: soft. guarding with palpation of abdomen. No palpable masses.
- GU: Tanner I female genitalia, clitoris nl. palpable inguinal lymphadenopathy.
- Neuro: sleepy but awakens to gentle stimulation, normal muscle tone, CN in tact. No tremor or dystonia. 3+ biceps/triceps and 4+ clonus at ankles.
- Skin: warm and dry. Discrete annular hyperpigmented papules with central clearing in diaper area, sacrum, and supraclavicular area. No acne, no striae.
Initial Laboratory Studies

Prior to HTN:
- Ca 10.7
- Mag 2.3
- Phos 5.5

With HTN:
- Ca 8.9
- Mag 2
- Phos 3
Additional Laboratory Studies

- **CBC**: WBC 8.4 (77% PMN), Hgb 12.4, MCV 63, Plt 455
- Cultures (CSF, Blood, stool, urine) (-); C. Diff (-)
- CSF (EBV, EV, HSV, VZV, CMV, TB): (-)
- ESR 29, CRP 10
- PT 12.1, INR 0.9, PTT 25.6
- Fibrinogen 409
- Uric Acid 7, LDH 463
- **UA**: 3+ protein, 2+ blood, 1+ ketones, (-) nitrite, (-) leukocyte esterase
Summary: Previously healthy 2 year 6 mo female

- 6 months mild weight loss
- 2 weeks polyuria, polydipsia
- 1 day of intractable emesis
- Hearing Loss
- Stiff neck, Incr DTRs, AMS
- Uncontrolled HTN following anesthetic
- AKI
- Hypernatremia
- Hypokalemia
- Hydrocephalus, ependymal thickening
- Parenchymal brain lesions
“Could this patient have a pheochromocytoma?”
Differential Diagnosis HTN

Mineralocorticoid Excess
- Aldosterone-secreting tumor
- Renin-secreting tumor
- CAH
- Adrenocortical Hyperplasia

Renovascular Disease
- Fibromuscular dysplasia
- Renal artery thrombosis

Catecholamine Excess
- Pheochromocytoma/Paraganglioma
- Neuroblastoma

• Renal parenchymal disease
- Coarctation of Aorta
- Hyperthyroidism
- Hypothyroidism

Hypercortisolism
- Cushing’s Syndrome
- Adrenocorticocarcinoma

• Essential HTN
Further Studies

- **Renal Ultrasound w/ Dopplers (performed twice):**
  - No renal artery occlusive disease
  - “Medical Renal Disease”
  - Smaller L kidney

- **R Renal Biopsy** -> Patchy tubular necrosis.

- **Echocardiogram:**
  - Structurally-normal heart
  - Wall thickness is normal
  - Cardiac function is normal
  - No coarctation of the aorta
## Hypertension Laboratory Evaluation

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal Range</th>
<th>HD # 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone</td>
<td>&lt; 40 ng/dL (supine)</td>
<td>170</td>
</tr>
<tr>
<td>Renin</td>
<td>1.4-7.8 ng/mL/hr</td>
<td>1110</td>
</tr>
</tbody>
</table>

- ACTH: 53.2 pg/mL
- Cortisol: 135.8 mcg/dL
- HVA (random urine): 5 mg/g Cr (range < 13.5)
- VMA (random urine): 5 mg/g Cr (range < 13)
## Hypertension Laboratory Evaluation

<table>
<thead>
<tr>
<th>URINE (24 hr)</th>
<th>Normal Range</th>
<th>HD # 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>900 mL</td>
<td></td>
</tr>
<tr>
<td>Normetanetphrines</td>
<td>&lt; 900 mcg (HTN)*</td>
<td>1215</td>
</tr>
<tr>
<td>Metanephrines</td>
<td>&lt; 400 mcg(HTN)*</td>
<td>477</td>
</tr>
<tr>
<td>Metanephrine, Total</td>
<td>57-210 (HTN)*</td>
<td>1692</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>4-29 mcg</td>
<td>46</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>&lt; 6.1 mcg</td>
<td>7.7</td>
</tr>
<tr>
<td>Dopamine</td>
<td>40-260 mcg</td>
<td>49</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PLASMA</th>
<th>Normal Range</th>
<th>HD # 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>70-750 pg/mL (supine)</td>
<td>3068</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>&lt; 111 pg/mL (supine)</td>
<td>437</td>
</tr>
<tr>
<td>Dopamine</td>
<td>&lt;30 pg/mL</td>
<td>166</td>
</tr>
</tbody>
</table>
Pheochromocytoma

- Very Rare: 1-2% of cases of secondary HTN in children
- 70% Adrenal medulla, 30% Extra-adrenal (paraganglioma)
- HTN is sustained in children vs. intermittent in adults

- Mechanisms for elevated renin:
  - Renin-secreting pheochromocytomas
  - Local compression of the renal artery by a perinephric mass
  - Catecholamine-induced renal vasoconstriction

Waguespack et al. 2010. JCEM.
Differential Diagnosis HTN

- **Mineralocorticoid Excess**
  - Aldosterone-secreting tumor
  - **Renin-secreting tumor**
  - CAH

- **Catecholamine Excess**
  - Pheochromocytoma/Paraganglioma
  - Neuroblastoma

- **Renovascular Disease**
  - Fibromuscular dysplasia
  - **Acute renal artery thrombosis**

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- Hyperthyroidism
- Hypothyroidism
- Hypercortisolism
- Essential HTN
Reninoma

- Even more rare than pheochromocytoma
- Benign juxtaglomerular tumor localized of kidneys
- Other tumors that are renin-secreting:
  - Wilm’s tumor, Renal cell carcinoma, Pheo
- Symptoms: Headache, polydipsia, polyuria, and myalgia
- Diagnosis:
  - Elevated Renin (20-274 mg/mL/hr) and Aldosterone (20-207 ng/dL)
  - Imaging: CT/MRI
  - Need pathology confirmation

Why, then, the excess in catecholamines?

Diker-Cohen et al. 2014. JCEM.
Gottardo et al. 2010. Urologia Internationalis.
Renin-angiotensin-aldosterone system

- Angiotensinogen
- Liver
- Decrease in renal perfusion (juxtaglomerular apparatus)
- Angiotensin I
- Angiotensin II
- Renin
- Kidney
- Surface of pulmonary and renal endothelium: ACE
- Lungs
- Kidney
- Sympathetic activity
- Tubular Na⁺ Cl⁻ reabsorption and K⁺ excretion, H₂O retention
- Adrenal gland: cortex
- Aldosterone secretion
- Arteriolar vasoconstriction, increase in blood pressure
- Pituitary gland: posterior lobe
- ADH secretion
- Collecting duct: H₂O absorption

Legend:
- Secretion from an organ
- Stimulatory signal
- Inhibitory signal
- Reaction
- Active transport
- Passive transport

Water and salt retention. Effective circulating volume increases. Perfusion of the juxtaglomerular apparatus increases.

http://en.wikipedia.org/wiki/Renin%28enzyme%29
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Abdominal MRI w/o contrast
Hospital Course Continued...

- BP Range 140’s-150’s/70’s-80’s:
  - Nitroglycerine 42 mcg/min IV
  - Nicardipine 3 mcg/kg/min IV
  - Amlodipine 10 mg BID
  - Lasix 12 mg q 12h IV
  - Losartan 0.7 mg/kg BID
  - Spironolactone 18 mg po BID
  - Phenoxybenzamine 1.2 mg/kg/day div. BID
  - Terazosin 2 mg po daily
- Progressive AKI (Creatinine ~ 3-4)
- Multiple thromboses at sites of prior PICC lines (RUE and LUE) and partial occlusion femoral artery -> started Heparin gtt
Further imaging

- MIBG?
  - I-131: Sens. 77-90%, Spec. 95-100%
  - I-123: Sens. 83-100%, Spec. 95-100% (limited availability)
  - Meds that interfere: Beta-blocker (72h) and CCB (48h)

- Somatostatin receptor scintigraphy?
  - More sensitive than MIBG for detecting smaller pheo and paraganglioma

- PET?
  - Non-specific
  - F-18 FDA > F-18 DOPA > F-18 FDG > MIBG for Pheo

PET Scan (FDG)
Peri-aortic mass resection

- **IR Angiogram:**
  - Identified *filling defect within the L renal artery* with supply to the kidney provided by branches proximal to the filling defect
  - Embolization of the left renal and adrenal artery

- Mass removed.
  - Pathology: *Left renal peri-hilar lymph node, negative for tumor*
Putting it all together...

- Acute renal artery thrombosis ->
- Activation of RAA system ->
  - Elevated renin and aldosterone
  - Moderate elevation in catecholamines
    - Exacerbated by stress
    - False-positive from Beta-blocker and CCB.
Brief report

Increased urinary catecholamines in a hypertensive child with renal artery stenosis

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What was the trigger?

- “Catastrophic Antiphospholipid Syndrome” or CAPS
- Variant of Antiphospholipid Syndrome (APS)
  - DVTs, Low platelets, Stroke/TIA, Fetal loss
  - = 1 clinical feature + antiphospholipid antibody x 2 (12 wks apart)
- CAPS = Widespread thrombotic disease
- Only 8/1000 pts with APS followed for 7 years developed CAPS
- Mortality approaches 50%
Rest of Course

- s/p retroperitoneal hematoma -> abdominal compartment syndrome, required laparotomy.
- Started plasmaphoresis and high-dose steroids for presumed CAPS, transitioned to Lovenox as outpatient.
- BP med wean: Diuril, Amlodipine, Clonidine, Lasix, Captopril. BP 122/59 in clinic last month.
- AKI improved, maintained good urine output.
Learning Points

- Consider causes of secondary hypertension in children with elevated BP.
- Pheochromocytoma and reninoma are both very rare causes of hypertension in children.
- Renal ultrasound has a low sensitivity for identifying renal artery stenotic lesions in children.
- Many medications and conditions can elevate catecholamines and cause false positive tests for pheochromocytoma.
- Some medications may interfere with radiotracer uptake with MIBG imaging for pheochromocytoma.
Works Cited