30 y.o female with low cortisol

Endorama

Thaer Idrees M.D.
First year adult endocrine fellow
I have no relevant financial relationships with any commercial interests
OBJECTIVES

• Symptoms, signs and laboratory findings of primary and secondary adrenal insufficiency
• Common etiologies for secondary adrenal insufficiency
• Less common etiologies for secondary adrenal insufficiency
30 yo F with PMH of STEMI (12/2017, balloon angioplasty to OM1 at NWH), R ulnar artery thrombosis, questionable hx of CVAs

CC: Diffuse bruising and abdominal pain

Consult: Low cortisol and low BP

- Generalized spontaneous bruising started 10 days PTA, predominantly on the legs. No trauma or falls, but on Plavix and stopped ASA recently
- Extreme epigastric pain started the day before along with severe headache and dizziness
- + photophobia, phonophobia, and nausea
PMH:
- STEMI 12/2017 NWM. OM1 s/p balloon angioplasty (unable to be stented)?dissection
- R ulnar arterial clot (after RUE swelling)
- Anxiety
- Strokes

PSH: None

PFH:
- Diabetes Maternal Grandfather
- High Cholesterol Maternal Grandfather
- Diabetes Paternal Grandfather
- High Cholesterol Paternal Grandfather
- High Cholesterol Father
- Hypertension Mother
- Heart Disease Maternal Grandfather
- Heart Disease Paternal Grandfather
- Hypertension Paternal Grandfather
- Hypertension Father
- Thyroid Disorder Maternal Grandmother
SH: Patient was born in India and raised in England. She completed graduate school in psychology.

PTA Meds:
Sertraline   Clonazepam   Atorvastatin
Buspar      Wellbutrin   Ambien PRN   Amlodipine

Allergies:
Colchicine, Norco
REVIEW OF SYSTEMS

- Constitutional: **Positive for malaise/fatigue and weight loss.** Negative for diaphoresis and fever.
- HENT: Negative for ear discharge, hearing loss and tinnitus.
- Eyes: Negative for blurred vision and double vision.
- Respiratory: Negative for cough, sputum production and shortness of breath.
- Cardiovascular: Negative for palpitations and claudication.
- Gastrointestinal: **Positive for abdominal pain, nausea and vomiting.** Negative for diarrhea.
- Genitourinary: Negative for dysuria.
- Musculoskeletal: **Positive for back pain and myalgias.** Negative for falls.
- Skin: Negative for rash.
- Neurological: Negative for dizziness, tingling, tremors, speech change and headaches.
- Endo/Heme/Allergies: Negative for environmental allergies.
- Psychiatric/Behavioral: Negative for depression. The **patient is nervous/anxious**.

All other systems reviewed and are negative.
PHYSICAL EXAM

• BP 90/53 | Pulse 80 | Temp (98.4 °F) | Resp 16 | Ht (5' 3") | Wt (128 lb) | SpO2 96% | BMI 22.68 kg/m2

• Constitutional: in moderate distress
• HEENT: EOMI, oropharynx clear
• Neck: supple, no thyromegaly, no acanthosis nigricans
• Cardiovascular: regular rate, no extra heart sounds
• Pulmonary/Chest: good respiratory effort, clear to auscultation bilaterally
• Abdomen: bowel sounds present, soft, tender, no violaceous straie, bruises
• Musculoskeletal: moving all extremities, bruises different ages.
• Neurological: sensation intact to light touch, strength 4/5 symmetrical
• Skin: warm, dry
• Psychiatric: not agitated, anxious
LABS

- CK 201
- Lipase 86
- Cortisol 0.7 (6 AM)
- Cortisol at NWMH 3 months PTA: 17

Adrenal crisis?
ACUTE ADRENAL INSUFFICIENCY

**Characteristics** | **Primary** | **Secondary**
--- | --- | ---
N, V, and abdominal pain | Prominent | Less common
Shock and low BP | XX | X
Hyperpigmentation (if acute on chronic) | XX | --
Fatigue and weakness | XX | XX
Low BG | XX | XX
Low Na | XX | X
High K | XX | --

Schrier et al., J Am Soc Nephrol. 2006

**Going back to the patient, what is the next step?**
### LABS

### Differential Diagnosis?

- Cortisol: 10.1 * ug/dL
- ACTH: 10.1

### Other labs?

- Estradiol, Serum: 46 *
- Luteinizing Hormone: 13.3 *
- FSH: 6.6 *

### Does report menstrual abnormalities for last 3 months
Headache
- Admitted few months ago with acute on chronic headache after a stroke. Reported only Dilaudid and morphine work
- Multiple admissions in the past at different institutions with headache that required Dilaudid
- Neurology: Topamax (patient did not use)

Bruising
- Hematology: negative work up including PT/PTT, fibrinogen, Factor VIII, paraneoplastic panel, vWD panel, D-dimer
- Hypercoagulable work up has been negative for anticardiolipin, vWF assay, anti-beta2-glycoprotein antibodies, lupus anticoagulant testing, normal PTG20210A and factor V, Protein C and S
- The only positive work up was high ANA (vascular purpura?) ➔ consult Rheumatology to r/o vasculitis

HOSPITAL COURSE
Rheumatology

- She had positive **ANA 1:1280**, but negative for dsDNA, anti-histone, Jo1, RF, ANCA, anticardiolipin IgG and IgM, B2GP IgG IgA IgM
- Less likely systemic vasculitis, no end-organ damage, no fever/ weight loss/ elevation of inflammatory markers to suggest an ongoing inflammatory process

Psych

- Significant domestic violence
The most common causes of secondary adrenal insufficiency are:
- Abrupt cessation of high-dose glucocorticoid therapy
- Correction (cure) of hypercortisolism (Cushing's syndrome)
OPIOIDS & ADRENAL INSUFFICIENCY

- Opiates may suppress the hypothalamic-pituitary-adrenal axis
- Eleven human studies suggested that long-term administration of opioids (oral, intravenous, or intrathecal) leads to suppression of the HPA axis
- Naloxone, an opioid receptor antagonist with a higher affinity for the $\mu$ receptor, given in high doses (>10 mg) to healthy volunteers increased cortisol levels and augmented corticotropin response to (CRH) stimulation

American College of Neuropsychopharmacology

Donegan et al., Mayo Clin Proc. 2018
<table>
<thead>
<tr>
<th>Drug</th>
<th>Authors</th>
<th>Year</th>
<th>Gender and Placebo</th>
<th>Route</th>
<th>Timing</th>
<th>Dose</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Allolio et al.</td>
<td>1987</td>
<td>6 Males and 1 female (placebo-controlled)</td>
<td>Oral</td>
<td>Single dose</td>
<td>30-mg slow release</td>
<td>Reduction in cortisol (124 vs 275 nmol/L), corticotropin (1.2 vs 2.9 pmol/L), and β-endorphin (28 vs 47 pmol/L) with decreased peak response to CRH</td>
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<td>Palm et al.</td>
<td>1997</td>
<td>5 (Double-blind, randomized, placebo-controlled, crossover)</td>
<td>Oral</td>
<td>1 wk</td>
<td>Day 1, 60 mg; day 2, 120 mg; day 3-7, 180 mg</td>
<td>Significant reduction in cortisol and corticotropin (24 vs 10 pg/mL) with reduced response in CRH stimulation (in 2 patients tested)</td>
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<tr>
<td></td>
<td>Abs et al.</td>
<td>2000</td>
<td>73 Received opioids and 20 chronic non-cancer pain-matched controls</td>
<td>Intrathecal</td>
<td>Long-term (mean, 26.6±16.3 mo)</td>
<td>Mean daily 4.8±3.2 mg (morphine, n=68; hydromorphone, n=5)</td>
<td>Decreased urinary free cortisol (36 vs 50.7 µg/L) and a reduced peak cortisol after ITT (245.4 vs 300.8 µg/L)</td>
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<td>Fentanyl</td>
<td>Oltmanns et al.</td>
<td>2005</td>
<td>1 (Case report)</td>
<td>Patch</td>
<td>2 y</td>
<td>480 mg</td>
<td>Adrenal crisis with reduced response to CRH</td>
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<td>Schimke et al.</td>
<td>2009</td>
<td>1 (Case report)</td>
<td>Patch</td>
<td>7 mo</td>
<td>180 mg</td>
<td>Secondary adrenal insufficiency with failure of cortisol to increase following corticotropin stimulation</td>
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<tr>
<td>Tramadol</td>
<td>Debono et al.</td>
<td>2011</td>
<td>1 (Case report)</td>
<td>Oral</td>
<td>3 y</td>
<td>15 mg</td>
<td>Low basal cortisol (54 ng/mL)</td>
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<tr>
<td>Opioid</td>
<td>Reference, year</td>
<td>No. of participants</td>
<td>MOA</td>
<td>Duration</td>
<td>Dose (MEDD)</td>
<td>Effect on HPA</td>
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<td>Mixed opioids</td>
<td>Gibb et al, 2016</td>
<td>48 Patients with</td>
<td>Oral: tramadol, oxycodone, morphine, or</td>
<td>Long-term (at least 6 mo</td>
<td>Median, 68 mg</td>
<td>4 (8.3%) patients had a basal cortisol level of &lt;100 nmol/L, 3 of whom had</td>
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<td>chronic noncancer</td>
<td>dihydroco-deine Patch: fentanyl or</td>
<td>use)</td>
<td>(40-153 mg)</td>
<td>inadequate response to corticotropin stimulation test</td>
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<td>pain (25 female and</td>
<td>buprenorphine</td>
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<td>Serum cortisol level was lower than the normal reference range in 3 patients</td>
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<td>23 male)</td>
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<td>(15%) and higher than normal range in 8 (40%) (reference range, 4.3-22.4 µg/dL). Corticotropin level was normal in 17 of 18 patients (94.5%) (reference range, 0-65 pg/mL)</td>
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<td>Merdin et al, 2016</td>
<td>20 Patients with</td>
<td>Not specified</td>
<td>Long-term (≥1 mo use)</td>
<td>Median, 180 mg/d (10-420 mg/d)</td>
<td>Peak corticotropin level following CRH was higher in the opioid-treated group than in controls (73.7 IE/L vs 39.2 IE/L) with no difference in basal or peak cortisol level</td>
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<td></td>
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<td>chronic cancer-</td>
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<td>associated pain</td>
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<td>Rhodin et al, 2010</td>
<td>39 Patients with</td>
<td>Methadone and slow-release morphine or</td>
<td>Long-term (&gt;1 y)</td>
<td>Mean in males treated with methadone, 1596 mg; and in females, 1322 mg</td>
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<td>chronic noncancer</td>
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<td>pain, 20 chronic</td>
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<td>noncancer controls</td>
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CONCLUSION

- Available data from small heterogeneous studies suggest that 9% to 29% of patients receiving long-term treatment with opiates have development of adrenal insufficiency.
- Careful consideration of OIAI in any patient receiving long term opiate therapy who manifests symptoms and signs suggestive of adrenal insufficiency.
BACK TO THE PATIENT

Imaging loading......
IMPRESSSION:
1. Disproportionate volume loss in the bilateral frontal lobes may indicate a neurodegenerative or developmental condition
2. Nonspecific small lesions (lacunar infarcts) in the bilateral frontal lobe white matter
3. No evidence of acute intracranial hemorrhage, mass, or acute infarct
The patient

Normal MRI from literature

IMPRESSION: no discernible pituitary lesions
The patient’s pituitary gland is small asymmetric and heterogenous, which consists with pituitary atrophy.

This is likely secondary to a remote pituitary infarct or resolved hypophysitis.

Given her cardiovascular risk factors, remote pituitary infarct is more likely.

While this could explain hypopituitarism, there is no actionable structural lesion or other surgical pathology, no evidence of tumor.
PITUITARY INFARCTION
(PITUITARY APOPLEXY)

• Pituitary adenomas are particularly prone to hemorrhage and necrosis
• Risk factors such as hypertension, medications, major surgeries, coagulopathies either primary or following medications or infection, head injury, radiation
• Vascular changes after pituitary irradiation often result in chronic hypoperfusion of the pituitary gland
• Even sometimes with coughing, or sneezing! (bleeding into an adenoma)

Bioussé et al., Journal of Neurology 2001
PITUITARY ATROPHY

Empty Sella syndrome

- Increased pressure in the suprasellar subarachnoid space or by reduction in the size of the pituitary gland
- Shrinkage of the pituitary gland may occur after post-partum pituitary necrosis (Sheehan’s syndrome) or pituitary infarction in patients with vascular diseases, diabetes, increased intracranial pressure, head injury, meningitis, or cavernous sinus thrombosis.
HYPOPHYSITIS

- AI: inflammatory infiltrate of the pituitary gland
- Symptoms of sellar compression, represented by headache and visual disturbances, are the most common and usually the initial complaint
- Symptoms are due to a partial or complete deficit of the anterior pituitary hormones, mainly ACTH followed by TSH, gonadotropins
- In contrast to other forms of hypopituitarism, ACTH deficiency is most common in patients with lymphocytic hypophysitis
- Over time the pituitary gland may atrophy, leaving an empty sella
All these patients had adenoma
BRAIN INJURY AND HYPOPITUITARY

- Anterior-pituitary dysfunction is more common than posterior-pituitary dysfunction in survivors of TBI
- In a meta-analysis, Schneider et al. included 1,015 TBI patients from ten cross-sectional and four prospective studies the pooled prevalence of anterior hypopituitarism has been reported as 27.5% (95% confidence interval 22.8–28.9)

Pathophysiology

- Long superior hypophyseal arteries provide the anterior pituitary gland with 70–90% of its blood supply (vulnerable to mechanical trauma, intracranial hypertension, low cerebral blood flow and brain swelling)
- Pituitary glands confinement within the bony sella

BIOTIN AND CORTISOL

- https://www.healthcare.uiowa.edu/path_handbook/Appendix/Chem/BiotinImmunoassayTables.pdf
BACK TO OUR PATIENT

Treatment plan
• Hydrocortisone 40 mg in AM and 20 mg in PM
• Decreased next day to 20 mg in AM and 10 mg in PM (blood pressure slightly improved)
• Started on Synthroid 25 mcg daily
• Was discharged on maintenance dose of hydrocortisone (20,10) and Synthroid
• Lost to follow up and missed endocrine appointment
REFERENCES

- UpTaoate: Causes of secondary and tertiary adrenal insufficiency in adults, Author:Lynnette K Nieman, MD
- JK Agarwal*, RK Sahay**, SK Bhadada**, Vijay Sekhar Reddy**, NK Agarwa , Empty Sella Syndrome,
THANK YOU

Questions/comments?