“A 42 Year Old Man with Flushing”

Dr. Dickens does not have any relevant financial relationships with any commercial interests. I will be discussing off label use of several medications for empiric treatment of flushing.
ENDORAMA:
A 42 Year Old Man with Flushing

Laura Dickens
September 6, 2018
Objectives

1. Discuss the differential diagnosis and evaluation of flushing
2. Understand the impact of neurologic disease on androgen function
3. Review specific and empiric treatments for flushing
Chief complaint

42 year old man referred from a community PCP to Endocrinology clinic with flushing
HPI

- For the past two years has had episodes of “hot flashes”
- Episodes occur 3-4 times per day and can be triggered by minor activity (washing dishes, crossing street) or heat
- Symptoms include flushing and facial sweating. He has seen that his face and neck are red at the time of symptoms. Episodes last 30 seconds to a few minutes
- Denies any specific triggers, foods, medications, anxiety, etc
- Denies associated symptoms of lightheadedness, palpitations, headaches, HTN
Past Medical History

- CVID- diagnosed in 2015, on IVIG
- Lung nodules, cough
  - Symptoms of cough and wheezing
  - Extensive evaluation including infectious and rheumatologic workup, bronch/EBUS (negative for infection or malignancy)
  - Treated briefly with empiric steroids without improvement
  - Mayo diagnosed “CVID related ILD (GLID)” and started azithromycin
- Huntington’s gene +
  - Family history of Huntington’s in his father
Review: Huntington’s Disease

- Inherited autosomal dominant neurodegenerative disorder
- Pathophysiology: CAG trinucleotide repeat expansion in the huntingtin (HTT) gene on chromosome 4p
- Clinical characteristics: choreiform movements, psychiatric symptoms, dementia
- Age of onset is determined by number of CAG repeats in HTT gene
  - <= 28 repeats is normal
  - 28-35 repeats – individual not affected, next generation at risk
  - 36-39 repeats – incomplete penetrance, late onset
  - >=40 repeats – disease will occur
Additional History

PSH: Inguinal hernia repair
ROS: +weight gain 50lbs in 2 years +fatigue +cough +wheezing +diarrhea 2-3 loose stools/day +flushing +loss of libido +absence of morning erections
Meds: Albuterol, Azithromycin, Breo inhaler (fluticasone-vilanterol), Nexium, Mucinex, multivitamin, vitamin C, coenzyme q10, fish oil
Allergies: Penicillin, Cephalexin
Social: Former smoker 1 ppd x6 years, quit in 2016. Two alcoholic drinks per week. No drugs. Recently moved in with girlfriend. Works as a forensic accountant. No pets, foreign travel, known environmental exposures.
Family: Huntington’s disease (father), hypertension (mother, brother)
Physical exam

VITALS: BP 113/85, HR 96, BMI 38.9

**General:** No apparent distress. He appears well developed and well nourished. Generally obese.

**HEENT:** NCAT. No pharyngeal erythema. PERRL. EOMI. No supraclavicular or dorsocervical fat pads.

**Neck:** No neck tenderness. No thyromegaly or palpable thyroid nodules

**CV:** Normal rate, regular rhythm. No edema.

**Pulm:** Clear bilaterally. No increased work of breathing, wheezes, rales.

**GI:** Soft, non-tender, non-distended abdomen. No rebound or guarding. No violaceous striae.

**MSK:** No deformities, no joint swelling. 5/5 strength and normal tone.

**Neuro:** A0x3, no focal deficits.

**Skin:** Fair skin. No rashes/ulcers, no facial acne.

**Psych:** Normal mood, thought content. Appropriate but anxious.
Labs

- Ca 9.6
- TSH 1.10
- Cortisol 10.2 (at 11am)
Flushing

- “A sensation of warmth accompanied by visible reddening of the skin”
- Heterogenous mechanisms
- Most prominent in face, neck, upper chest and arms
- Episodic or constant

Considering his constellation of symptoms, what would you order first?
Flushing: Differential Diagnosis

**Table II. Differential diagnosis of flushing**

<table>
<thead>
<tr>
<th>Common causes</th>
<th>Uncommon, serious causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign cutaneous flushing</td>
<td>Carcinoid</td>
</tr>
<tr>
<td>Emotion</td>
<td>Pheochromocytoma</td>
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<tr>
<td>Temperature</td>
<td>Mastocytosis</td>
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<tr>
<td>Food or beverage</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Rosacea</td>
<td>Other causes</td>
</tr>
<tr>
<td>Climacteric flushing</td>
<td>Medullary thyroid carcinoma</td>
</tr>
<tr>
<td>Fever</td>
<td>Pancreatic cell tumor (VIP tumor)</td>
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<tr>
<td>Alcohol</td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td>Uncommon, serious causes</td>
<td>Fish ingestion</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Histamine</td>
</tr>
<tr>
<td>Parkinson’s</td>
<td>Ciguatera</td>
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<tr>
<td>Migraine</td>
<td></td>
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<tr>
<td>Multiple sclerosis</td>
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<tr>
<td>Trigeminal nerve damage</td>
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<tr>
<td>Horner syndrome</td>
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<tr>
<td>Frey syndrome</td>
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<tr>
<td>Autonomic epilepsy</td>
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<tr>
<td>Autonomic hyperreflexia</td>
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<tr>
<td>Orthostatic hypotension</td>
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<tr>
<td>Streeter syndrome</td>
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<tr>
<td>Medications (see Table IV)</td>
<td></td>
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<tr>
<td>Very rare causes</td>
<td></td>
</tr>
<tr>
<td>Psychiatric or anxiety disorders</td>
<td>Sarcoïd, mitral stenosis, dumping syndrome,</td>
</tr>
<tr>
<td>Idiopathic flushing</td>
<td>male androgen deficiency, arsenic intoxication,</td>
</tr>
<tr>
<td>Neurologic</td>
<td>POEMS syndrome, basophilic granulocytic leukemia,</td>
</tr>
<tr>
<td>Parkinson’s</td>
<td>bronchogenic carcinoma, malignant histiocytoma,</td>
</tr>
<tr>
<td>Migraine</td>
<td>malignant neuroblastoma, malignant</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>ganglioneuroma, peri-aortic surgery,</td>
</tr>
<tr>
<td>Trigeminal nerve damage</td>
<td>Leigh syndrome, Rovsing syndrome</td>
</tr>
</tbody>
</table>

Carcinoid Syndrome

- Associated with NET in the GI tract and lungs
- Most common with disseminated disease and liver metastases
- Causative secretory products include:
  - Serotonin \(\rightarrow\) causes diarrhea and fibrosis, not flushing
  - Histamine, tachykinins, kallikrein, and prostaglandins

Symptoms:
- Flushing (85%) ✓
- Venous telangiectasia
- Diarrhea (80%) ✓
- Bronchospasm (10-20%) ✓
- Cardiac valvular lesions

Diagnosis
- 24 hour 5-HIAA
  - 90% sensitive and specific
- Chromogranin not recommended for screening
Instructions for urine 5-HIAA testing

• Certain foods and medications are associated with falsely high and low values for urinary 5-HIAA
• Counsel patients to avoid these for 3 days prior to 24 hour urine collection
• Dot phrase: LDLABHIAA
Lab results

24 hour urine 5-HIAA = 4.3 (reference <=8.0)

What next?
Flushing: Evaluation

Additional labs

• TSH = 1.64
• Free T4 = 1.10
• Calcitonin- negative
• 24 hour urine metanephrines- normal
• Testosterone (8:10am)
  – Te binding globulin 21
  – Free testosterone 64 pg/mL
  – Total testosterone 167 ng/dL
• Tryptase = 6.3 ng/mL (reference <11.5)
• VIP <50 pg/mL (reference <75)
Additional Labs

• Testosterone (7:47am)
  – Te binding globulin 23
  – Free testosterone 39 pg/mL
  – Total testosterone 128 ng/dL
• LH 4.7
• FSH 5.2
• Prolactin 11.82 ng/mL
• Iron studies – normal

How would you characterize his hypogonadism?

What additional labs and studies would you order?
MRI Pituitary

FINDINGS: There is a 6mm diameter T1 hyperintense lesion with fluid signal intensity on T2-weighted images with central low signal intracystic nodule in the left pituitary. There is an additional punctate T1 hyperintense focus in the pituitary gland anterior to the usual location of the posterior pituitary bright spot. There is compression of the adjacent pituitary gland. The pituitary stalk lies midline. The supracellar cistern, optic chiasm, cavernous sinuses, and intracranial portions of the optic nerves appear unremarkable

IMPRESSION:
- A 6mm lesion in the left pituitary highly suggestive of Rathke’s cleft cyst
- Additional punctate focus may represent another Rathke’s cleft cyst
What is the likely etiology of his hypogonadism?
Androgen function and pathophysiology/treatment of male Huntington’s Disease patients

- MRI has shown hypothalamic atrophy as an early finding in HD
- Highest Huntington gene expression seen in brain and testes
- Mouse models
  - R6/2 HD: decrease in GnRH secreting neurons -> hypogonadotropic hypogonadism
  - YAC 128 HD: testicular atrophy with normal testosterone

Testosterone levels in male patients with Huntington’s Disease

- 42 men with Huntington’s Disease (HD) compared to age-matched controls
- Compared plasma total testosterone, LH, FSH

Results:
- HD patients had significantly lower testosterone levels
- 35.7% of HD patients had total testosterone (TT) level <200 ng/dl
- LH levels reduced in HD patients, correlation to TT not significant
- Testosterone level correlated to disease severity in HD patients

Testosterone levels in male patients with Huntington’s Disease

Back to our patient

<table>
<thead>
<tr>
<th>Date</th>
<th>Free Testosterone</th>
<th>Total Testosterone</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/28/16</td>
<td>140</td>
<td>346</td>
<td>Androgel 50mg daily</td>
</tr>
<tr>
<td>1/17/17</td>
<td>451</td>
<td>945</td>
<td>Androgel 75mg daily</td>
</tr>
<tr>
<td>3/14/17</td>
<td>146</td>
<td>381</td>
<td>Androgel 50mg daily</td>
</tr>
</tbody>
</table>

Clinic follow up

- Energy and libido improved
- Flushing no different
- What would you do next?
Targeted Treatment of Flushing

• Benign cutaneous flushing
  – Biofeedback, hypnosis, nonselective beta-blocker (Nadalol, Propranolol)
• Menopausal flushing
  – SSRI, SNRI, gabapentin, pregabalin, clonidine
• Carcinoid syndrome → Cyproheptadine, H1/H2 receptor antagonists
• Mastocytosis → H1/H2 receptor antagonists, disodium cromoglycate
• Niacin-induced flushing → Aspirin 325mg, 30 minutes before dose
• Rosacea → multiple therapies attempted, none consistently effective
Hot Flashes in Men on ADT for Prostate Cancer

- Related to sudden change sex steroid levels, which alters function of multiple neurotransmitters leading to thermoregulatory instability
- Hot flushes are reported in 34–80% of men who have been treated with anti-androgen therapy for prostate cancer and up to 27% report this symptom to be the most troublesome adverse effect
- Testosterone is contraindicated
- Treatment options:
  - Megestrol acetate
  - Cyproterone- 94.5% decrease in hot-flush score
  - Medroxyprogesterone- 83.7% decrease in hot-flush score
  - Venlafaxine- 47.2% decrease in hot-flush score
  - Gabapentin- RCT showed a moderate effect
- Hormonal treatments most effective but with significant side effects (gynecomastia, weight, appetite)
Patient Course

- **Empiric flushing treatment**
  - Off-label **Non-selective beta blocker** contraindicated with history of obstructive lung disease
  - Off-label Recommended **Aspirin** 325mg daily → ineffective
  - Off-label Recommended **SSRI** → he previously took citalopram without effect
  - Off-label Recommended **Gabapentin** → patient declined
  - Off-label Last visit started **Clonidine patch** → will follow up next month

- **GL-ILD** being treated by a specialist in Milwaukee with Rituximab and cellcept
- Specialized PT program for Huntington’s at NWMH, reportedly showing subtle motor signs of the disease
Questions?

Thank you!
References

- UpToDate. Clinical features of the carcinoid syndrome
- UpToDate. Diagnosis of the carcinoid syndrome and tumor localization.