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MEDICINE &
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SCIENCES

“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

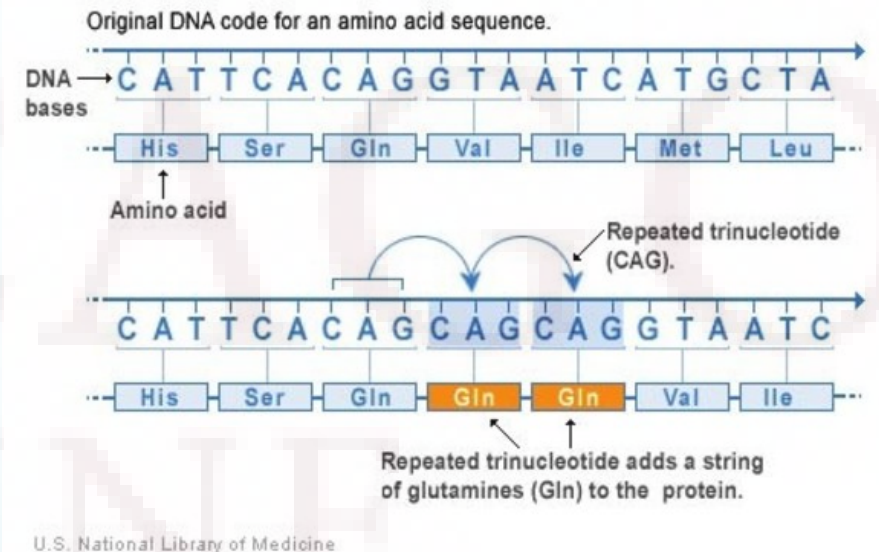
Past Medical History

- 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

Repeat expansion mutation



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.

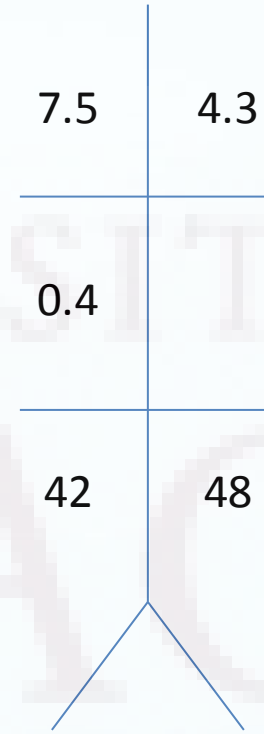
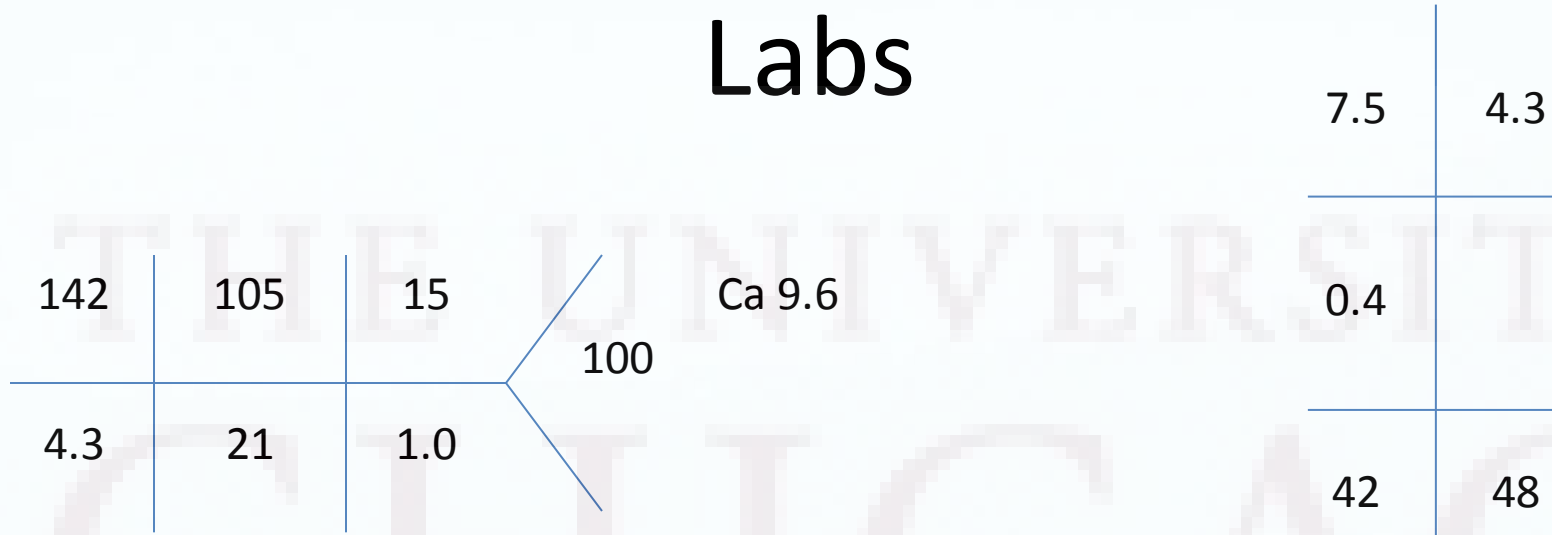
MSK: No deformities, no joint swelling. 5/5 strength and normal tone.

Neuro: AOx3, no focal deficits.

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

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

Labs



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

Table I. Pharmacologic mediators of flushing

Foods, beverages, alcohol
Tyramine, histamine, sulfites, nitrites, alcohol, aldehyde, higher chain alcohols, monosodium glutamate, capsaicin, cigua toxin (fish)
Climacterium
Estrogen fluctuations
Carcinoid syndrome
5-HT (no flushing but diarrhea), substance P, histamine, catecholamines, prostaglandins, kallikrein, kinins, tachykinins, neurotensin, neuropeptide K, VIP, gastrin-related peptide, motilin
Pheochromocytoma
Catecholamines (epinephrine, norepinephrine, dopamine), VIP, calcitonin-gene-related peptide, adrenomedullin
Mastocytosis
Histamine, prostaglandin D ₂ , leukotrienes, tumor necrosis factor α , vascular endothelial growth factor, interleukins, heparin, acid hydrolases
Anaphylaxis
Histamine, other mast cell and basophil mediators, as above for mastocytosis
Medullary carcinoma of the thyroid
Calcitonin, prostaglandins, histamine, substance P, levodopa, ketacalcin, adrenocorticotrophic hormone, corticotropin-releasing hormone
Pancreatic cell carcinoma
VIP, prostaglandin, gastric inhibitory polypeptide
Renal cell carcinoma
Prostaglandins, pituitary down-regulation
Neurologic
Substance P, catecholamines



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Considering his constellation of symptoms,
what would you order first?

Flushing: Differential Diagnosis

Table II. Differential diagnosis of flushing

Common causes

Benign cutaneous flushing

Emotion

Temperature

Food or beverage

Rosacea

Climacteric flushing

Fever

Alcohol

Uncommon, serious causes

→ Carcinoid

Pheochromocytoma

Mastocytosis

Anaphylaxis

Other causes

Medullary thyroid carcinoma

Pancreatic cell tumor (VIP tumor)

Renal cell carcinoma

Fish ingestion

Histamine

Ciguatera

Psychiatric or anxiety disorders

Idiopathic flushing

Neurologic

Parkinson's

Migraine

Multiple sclerosis

Trigeminal nerve damage

Horner syndrome

Frey syndrome

Autonomic epilepsy

Autonomic hyperreflexia

Orthostatic hypotension

Streeten syndrome

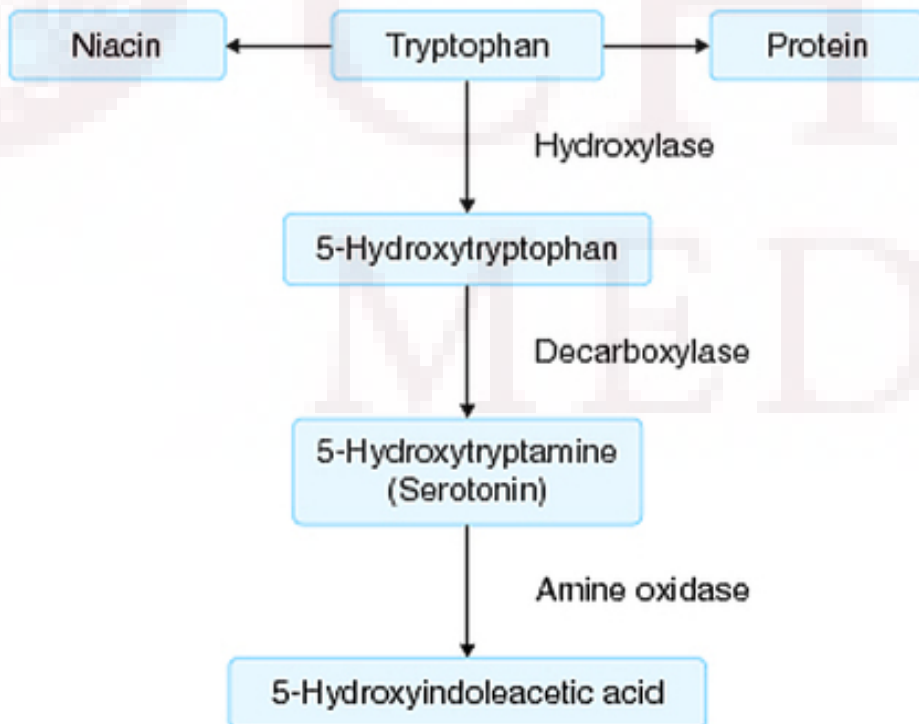
Medications (see [Table IV](#))

Very rare causes

Sarcoid, mitral stenosis, dumping syndrome, male androgen deficiency, arsenic intoxication, POEMS syndrome, basophilic granulocytic leukemia, bronchogenic carcinoma, malignant histiocytoma, malignant neuroblastoma, malignant ganglioneuroma, peri-aortic surgery, Leigh syndrome, Roving syndrome

Carcinoid Syndrome

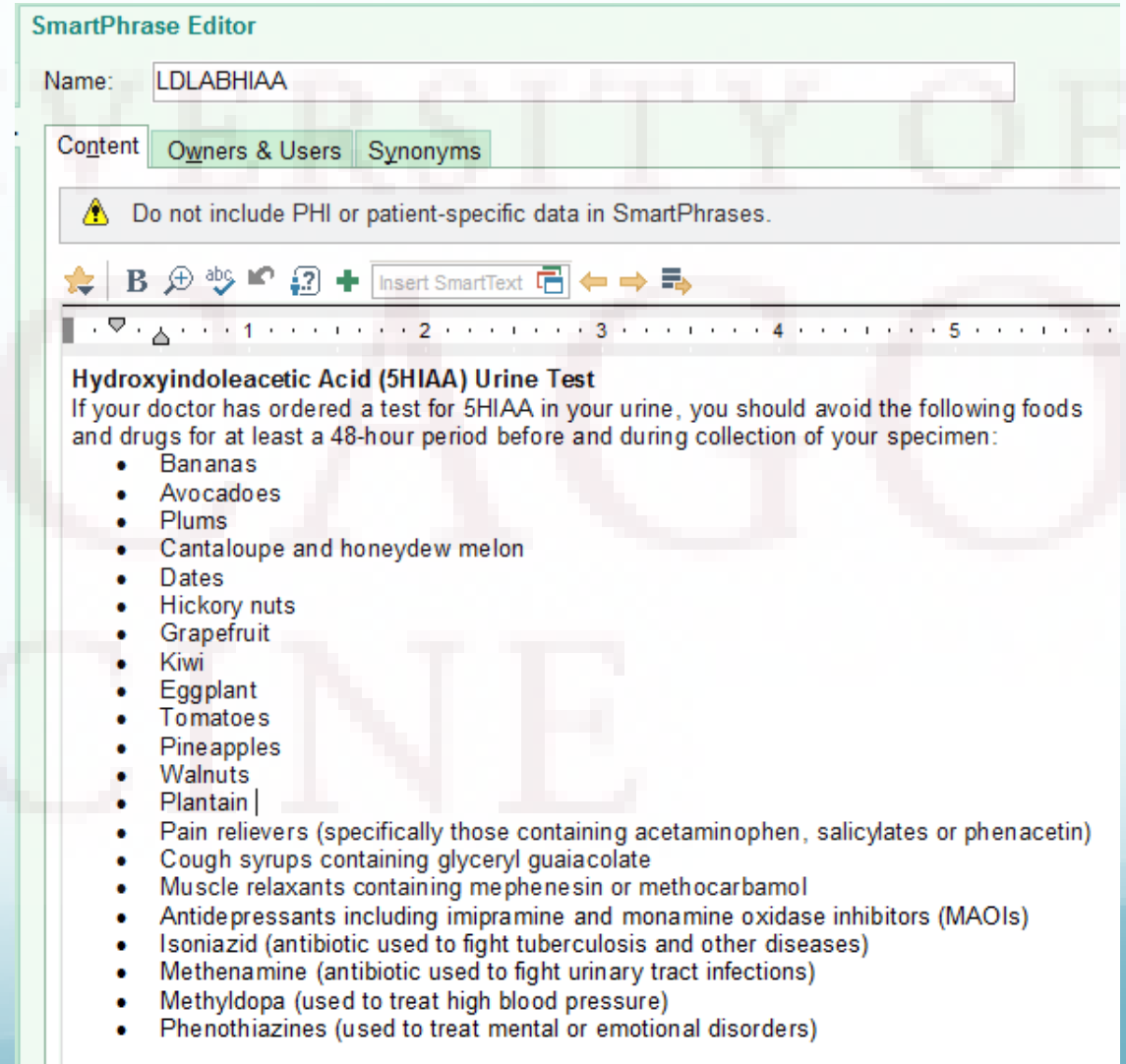
- Associated with NET in the GI tract and lungs
- Most common with disseminated disease and liver metastases



- 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













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Content **Owners & Users** Synonyms

 Do not include PHI or patient-specific data in SmartPhrases.

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Hydroxyindoleacetic Acid (5HIAA) Urine Test

If your doctor has ordered a test for 5HIAA in your urine, you should avoid the following foods and drugs for at least a 48-hour period before and during collection of your specimen:

- Bananas
- Avocadoes
- Plums
- Cantaloupe and honeydew melon
- Dates
- Hickory nuts
- Grapefruit
- Kiwi
- Eggplant
- Tomatoes
- Pineapples
- Walnuts
- Plantain |
- Pain relievers (specifically those containing acetaminophen, salicylates or phenacetin)
- Cough syrups containing glyceryl guaiacolate
- Muscle relaxants containing mephenesin or methocarbamol
- Antidepressants including imipramine and monamine oxidase inhibitors (MAOIs)
- Isoniazid (antibiotic used to fight tuberculosis and other diseases)
- Methenamine (antibiotic used to fight urinary tract infections)
- Methyldopa (used to treat high blood pressure)
- Phenothiazines (used to treat mental or emotional disorders)

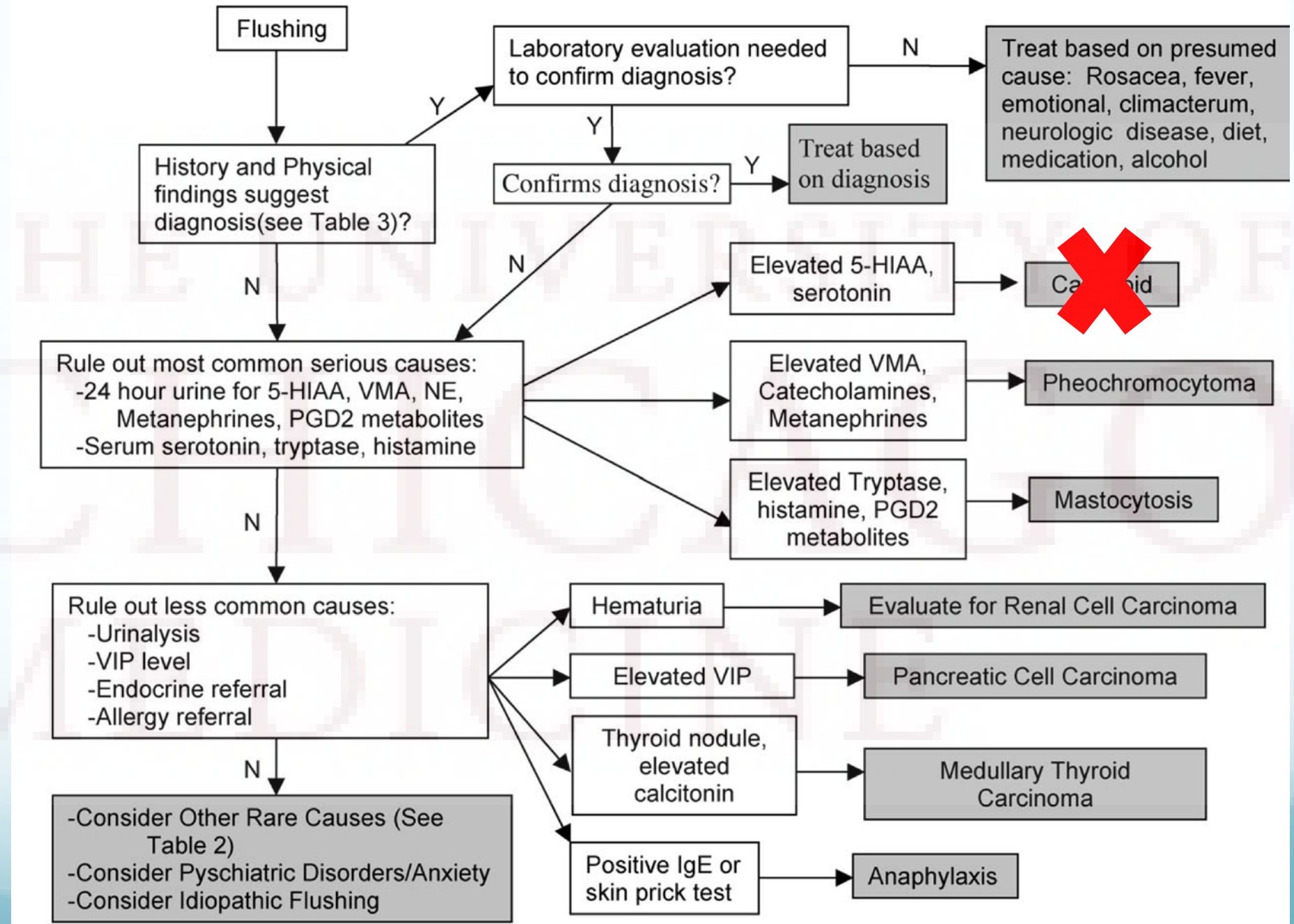
Lab results

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

What next?

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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)
 - Testosterone 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?

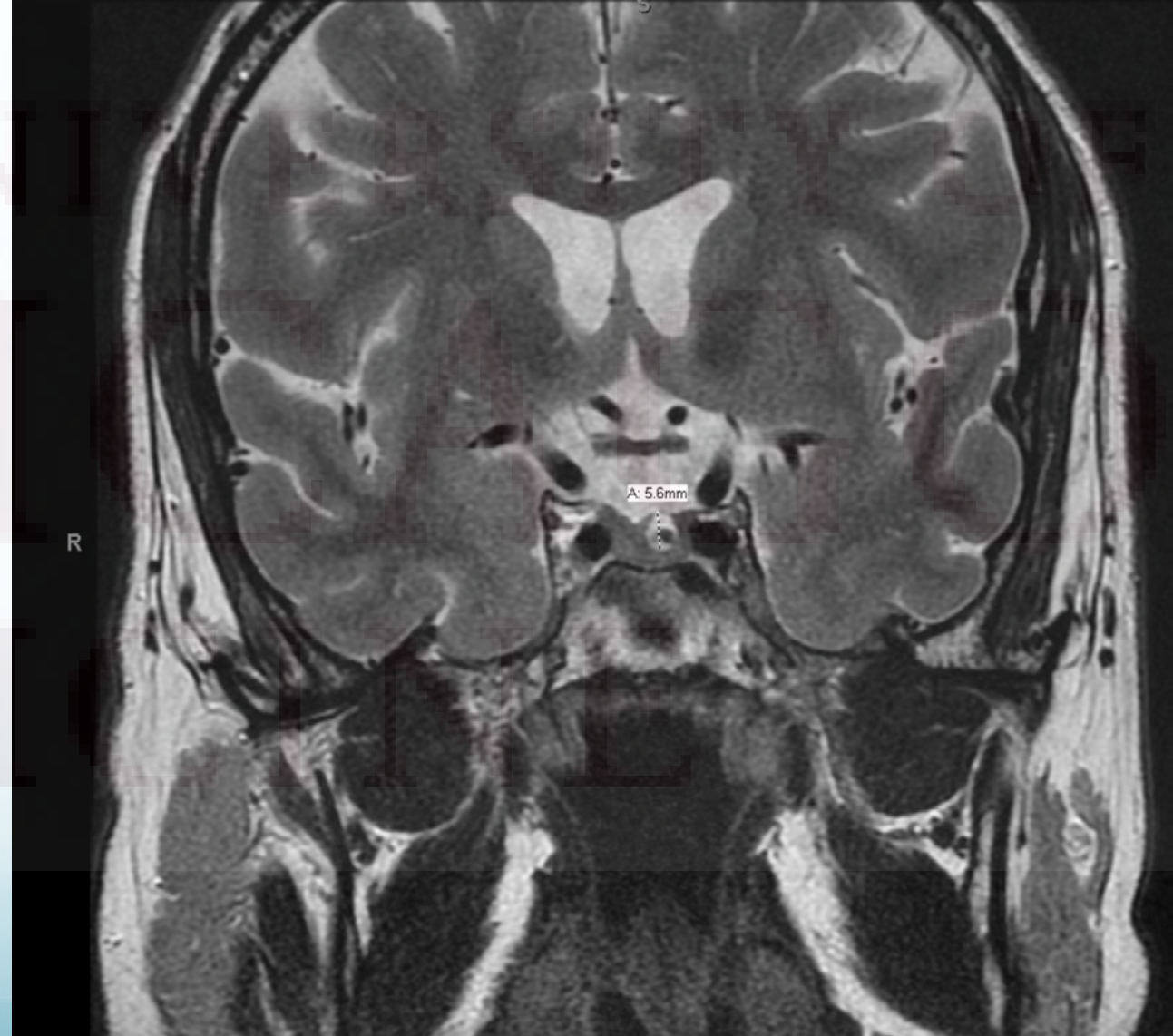
What additional labs and studies would you order?

MRI Pituitary wwo

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



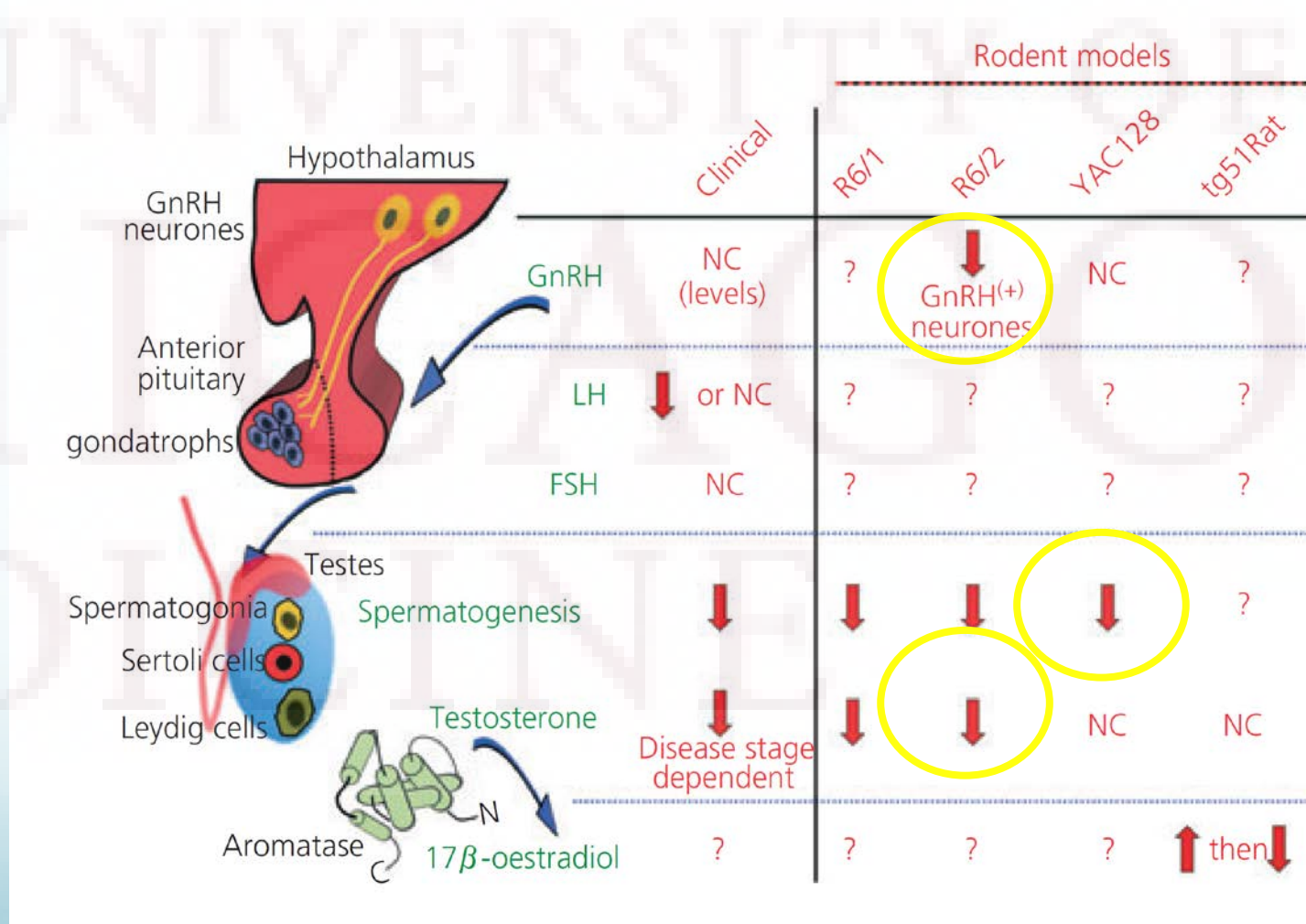


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What is the likely etiology of his hypogonadism?

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



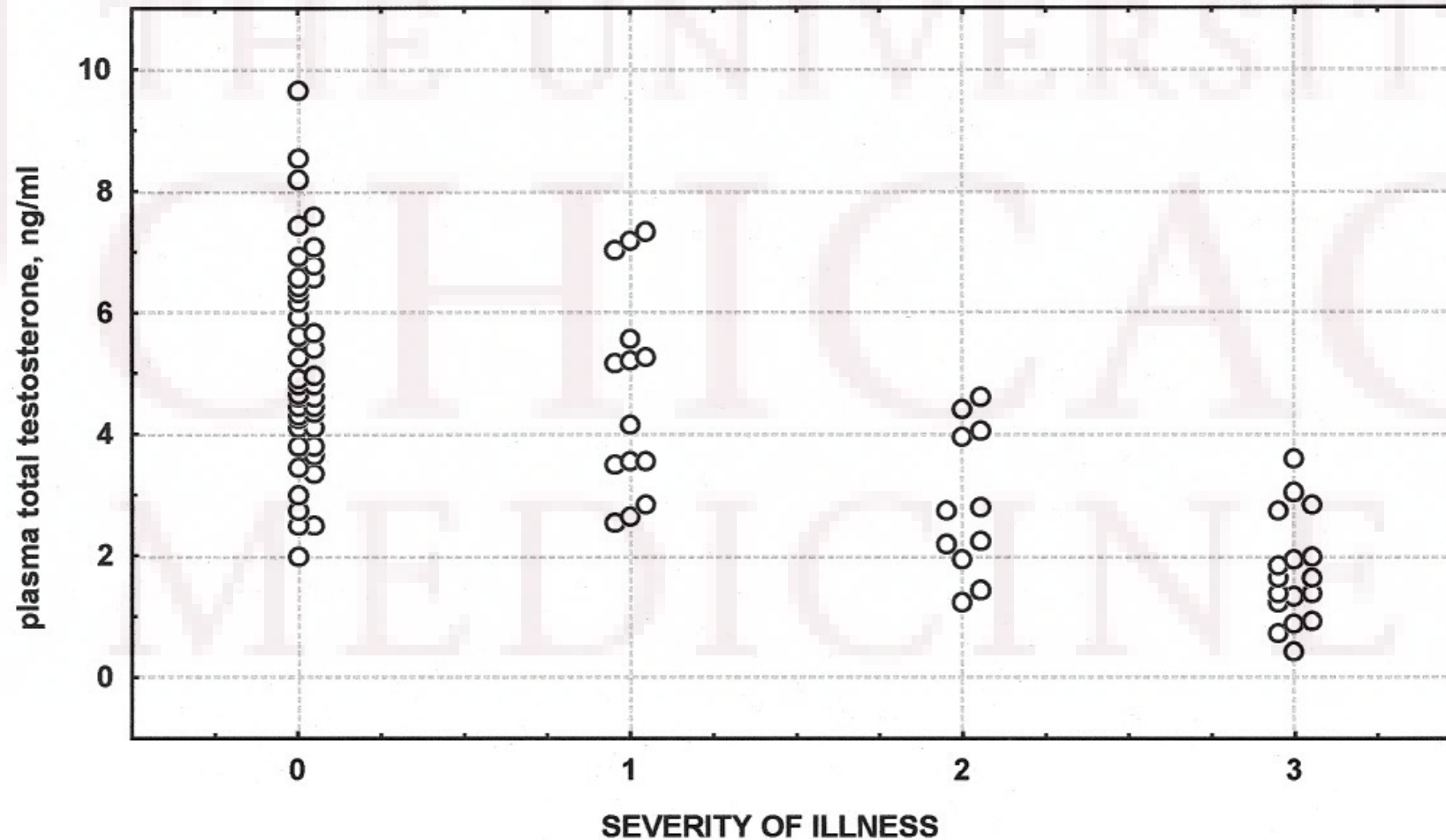
Testosterone levels in male patients with Huntington's Disease

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

Table 3. Analysis of the Hormone Data in Relation to the Severity of Illness of the Patients

Severity	N	Age	Age at Onset	Duration	CAG Repeats	Testosterone	LH	FSH
Controls	44	48.9 ± 13.0				4.91 ± 1.65	2.69 ± 1.05	3.97 ± 1.96
1, mild	14	49.4 ± 12.6	44.8 ± 9.8	4.6 ± 6.5	44.3 ± 3.2	4.67 ± 1.68	2.12 ± 0.90	4.24 ± 2.13
2, moderate	11	44.4 ± 8.8	40.4 ± 7.9	4.0 ± 7.9	47.0 ± 4.8	2.86 ± 1.21	1.63 ± 0.65	3.35 ± 1.29
3, severe	17	55.8 ± 12.3	45.6 ± 9.2	10.2 ± 5.9	44.6 ± 3.5	1.73 ± 0.88	2.61 ± 1.32	4.41 ± 2.82
F			1.18	5.43	1.88	21.96	3.28	0.34
p			0.32	0.008	0.17	0.0000	0.025	0.79

Testosterone levels in male patients with Huntington's Disease



Back to our patient

	11/28/16	1/17/17	3/14/17
Free testosterone	140	451	146
Total testosterone	346	945	381
	Androgel 50mg daily	Androgel 75mg daily	Androgel 50mg daily

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)

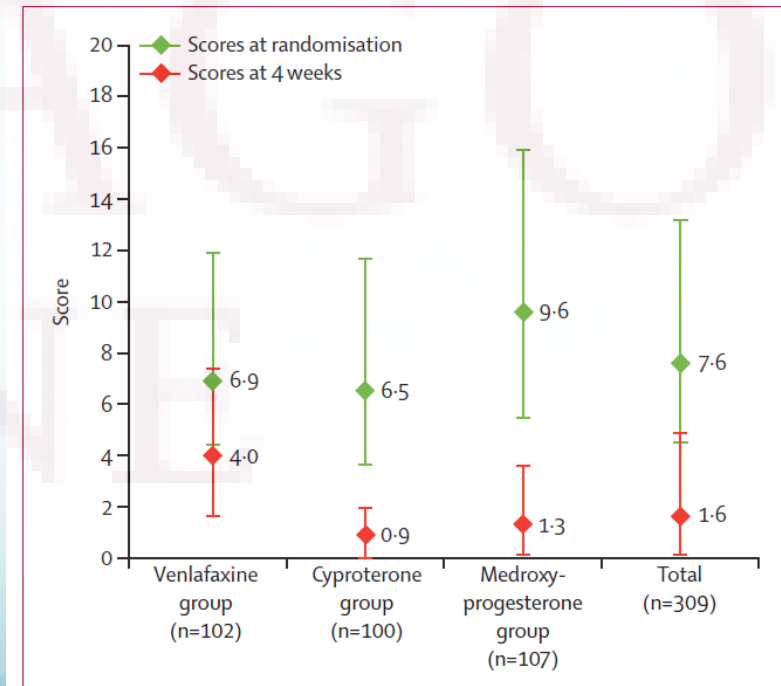


Figure 2: Median daily hot flush score according to randomisation group
Bars represent the IQR.

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



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Questions?
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Thank you!
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