67 y.o. female with bilateral flank pain

Endorama, 01/17/2013,
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History of past illness:

- 67 y.o. female presented to her PCP with c/o bilateral flank pain off and on for the last 8 months. Pain was dull, boring, 3-4/10, was better with urination. No associated hematuria or dysurea. Kidney US was ordered and the pt was referred to nephrology for further evaluation.

- Kidney US showed: bilateral slightly echogenic kidneys. Right simple renal cyst. Indeterminate exophytic right upper pole lesion. A solid renal or adrenal neoplasm can not be excluded. MRI of the kidneys is recommended for further evaluation.

Past medical history:

- HTN
- DM2
- CKD stage 4
- Hyperlipidemia
- Osteoarthritis of her knees
- Ischemic stroke in 04/2011
- Lumbar stenosis

- **Ob&Gyn:** Menarche at 11 years old, menstrual cycles are regular, every month, had 4 spontaneous pregnancies, all ended with miscarriages in the first trimester. Menopause at 47 years old.

- **Medications:** Chlorthalidone 50mg/day, Dilthiazem ER 240mg/day, Lantus 10 units/day, lisinopril 40mg/day, Saxagliptin 2.5mg/day, simvastatin 10mg QHS, tramadol 50mg Q6H PRN pain.

- **Family history:** No history of adrenal nodules, no fertility problems, no diabetes or thyroid problem. Father died in his 90`s from ,,natural,, causes. Mother died from a stroke in her 60`s. Does not have any siblings.

- **Social history:** retired from clerical work, unmarried, lives alone, has no children, hx of marijuana and cocaine abuse (last in 2006). Currently does not smoke, drink alcohol or use any illegal drugs.

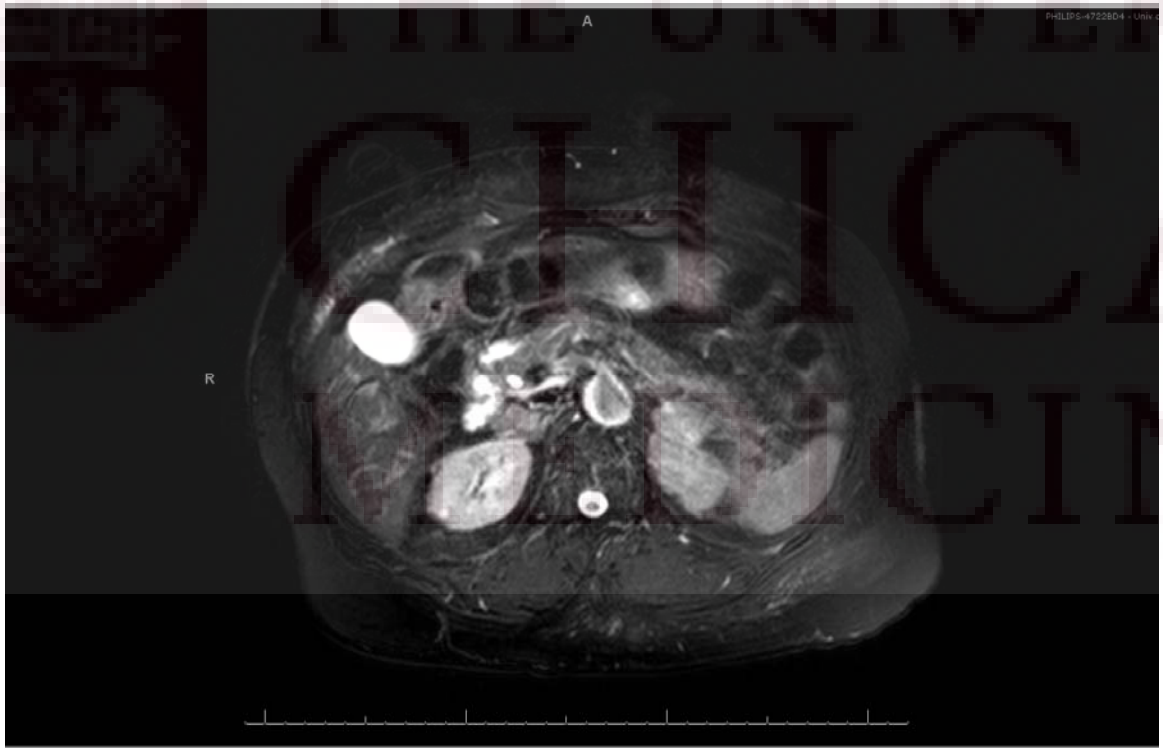
Review of systems:

- Constitutional: No fevers. No weight loss. **+Fatigue.**
- HEENT: No vision changes. No hoarseness. Neck: No neck swelling or pain.
- Cardiovascular: No chest pain. No palpitations.
- Respiratory: No dyspnea. No orthopnea.
- Gastrointestinal: No diarrhea. No constipation.
- Musculoskeletal: No muscle pain. No LE edema.
- Genitourinary: **Menopause since the age of 47. Bilateral flank pain.**
- Skin: No rash. No skin changes. No hair loss.
- Neurologic: No tremor. No headache. No weakness.
- Psychiatric: No depression. No anxiety. Endo: No polyuria. No polydypsia.

Physical exam:

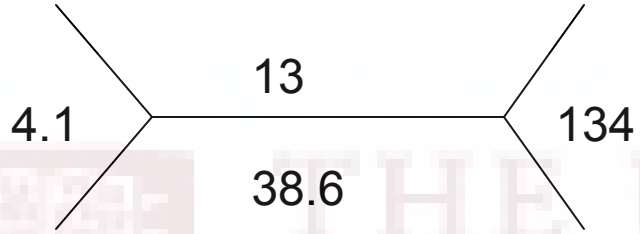
- Vitals: height 167.6 cm (5' 6"), weight 81.557 kg (179 lb 12.8 oz), BMI 29.02, BP 165/97, HR 80, RR18.
- Head: Normocephalic and atraumatic.
- Mouth/Throat: Oropharynx is clear and moist. No oropharyngeal exudate.
- Eyes: EOM are normal. Pupils are equal, round, and reactive to light. No scleral icterus.
- Neck: Normal range of motion. Neck supple. No JVD present**.** No tracheal deviation present. No thyromegaly present.
- Cardiovascular: Regularly heart rate and rhythm, normal heart sounds and intact distal pulses. No friction rub. No murmur heard.
- Pulmonary/Chest: Bilateral crackles. Moderate respiratory distress. No wheezes. No rales. No tenderness.
- Abdominal: Soft. Bowel sounds are normal. No distension and no mass. There is no tenderness. There is no rebound and no guarding. Swollen abdominal wall. **No stretch marks.**
- Musculoskeletal: Normal range of motion. No cervical adenopathy. **No CVA tenderness on palpation.**
- Neurological: She is alert and oriented to person, place, and time. No cranial nerve deficit. Normal muscle tone. Coordination normal. Brisk reflexes in upper and lower extremities. No LE edema.
- Skin: Skin is warm. Not diaphoretic. No erythema. No pallor. Psychiatric: normal mood and affect, behavior is normal. Judgment and thought content normal.

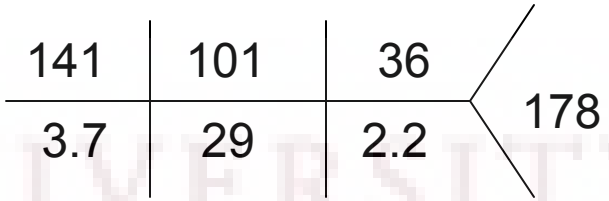
MRI of the abdomen with adrenal wash out protocol:



Nodular enlargement of both adrenal glands. The medial limb of the right adrenal gland measures 4.8 x 2.1 cm. Both limbs of the left adrenal gland are enlarged and nodular. The medial limb measures 5.5 x 2.6 cm. Both masses have homogenous loss of signal on out of phase images, compatible with fat. These findings may represent macronodular adrenal hyperplasia or multiple large, bilateral adrenal adenomas.

Labs:





Ca 9.7 (8.4 - 10.2 mg/dL)

HA1C 7.8%

ACTH (random) <5.0 pg/mL

Cortisol (random) 20.5 mcg/dL

Aldosterone 15 ng/dL (<=21 ng/dL)

Renin 3.2 ng/mL/h (<=0.6-3.0 ng/mL/h)

Normetanephrine 0.82 nmol/L (<0.90 nmol/L)

Metanephrine 0.22 nmol/L (<0.50 nmol/L)

24hr urine collection:

Total volume 600ml

Creatinine 600mg (800 - 1800 mg/24hrs)

Normetanephrine 152 mcg (138-521 mcg (Normotensive), <900 mcg (Hypertensive))

Metanephrine 207 mcg (171-616 (Normotensive) <1300 (Hypertensive))

1mg dexamethasone suppression test:

Cortisol (8AM) 19.4 mcg/dL

Dexamethasone: 532 ng/dL (1 mg dexamethasone overnight: 180-550 (8:00-10:00 AM)

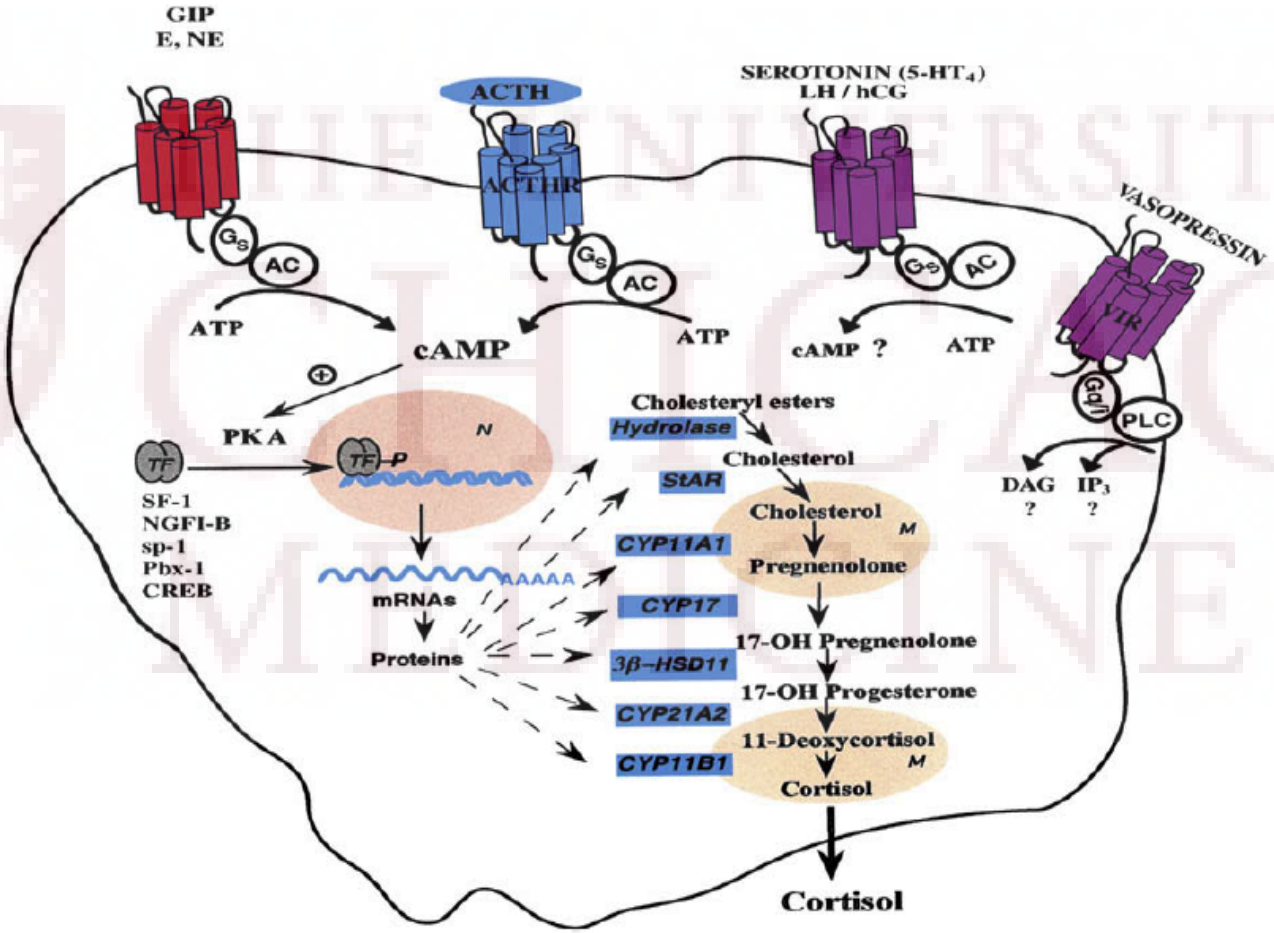
- What is bilateral nodular adrenal hyperplasia?
- How it should be evaluated?
- What is the management?

- Bilateral macronodular adrenal hyperplasia is a rare cause of Cushing syndrome, as it is estimated to represent less than 1% of endogenous cases
- It is associated with adrenal glands weighing from 24 to 500 g that contain multiple nonpigmented nodules greater than 5 mm in diameter
- Most patients present in the fifth and sixth decades
- The most frequent variant of bilateral macronodular hyperplasia - pigmented nodular adrenocortical disease, which may be sporadic or familial (as part of the Carney complex – myxomas of the heart and skin, hyperpigmentation of the skin, pigmented nodular adrenocortical disease)

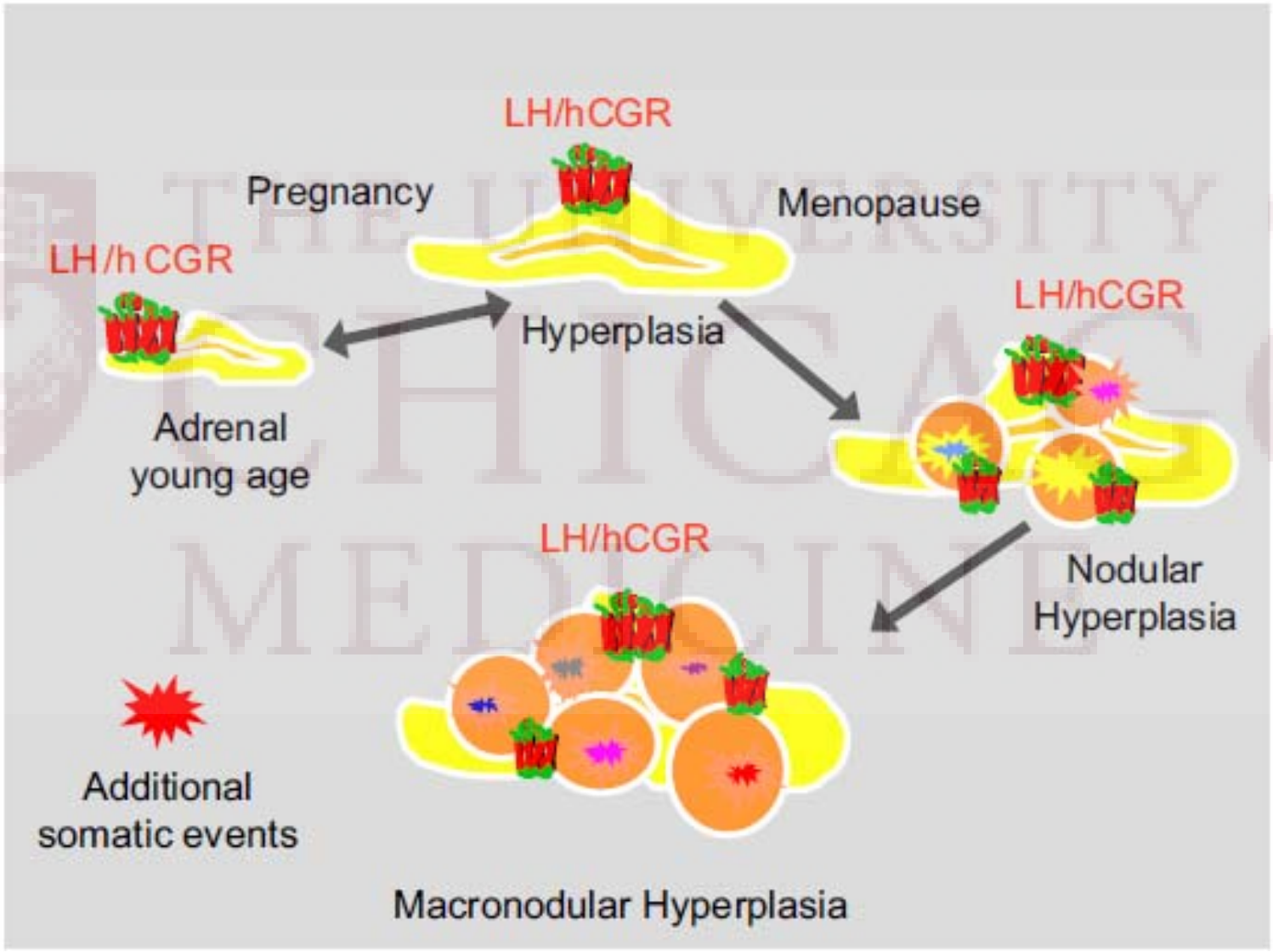
Pathogenesis:

- aberrant hormone receptors
- genetic mutations

Aberrant receptors:



Aberrant LH/hCG receptors:



Genetic causes:

- Gs alpha-subunit mutations (Cushing's syndrome associated with McCune-Albright syndrome)
- MC2R gene mutations: activating mutations of the ACTH receptor
- MEN1: caused by mutations in the tumor suppressor gene menin
- Other genes: mutation in the adenomatous polyposis coli gene (associated with polyposis coli syndrome), fumarate hydratase gene (associated with hereditary leiomyomatosis and renal cell cancer)

Evaluation:

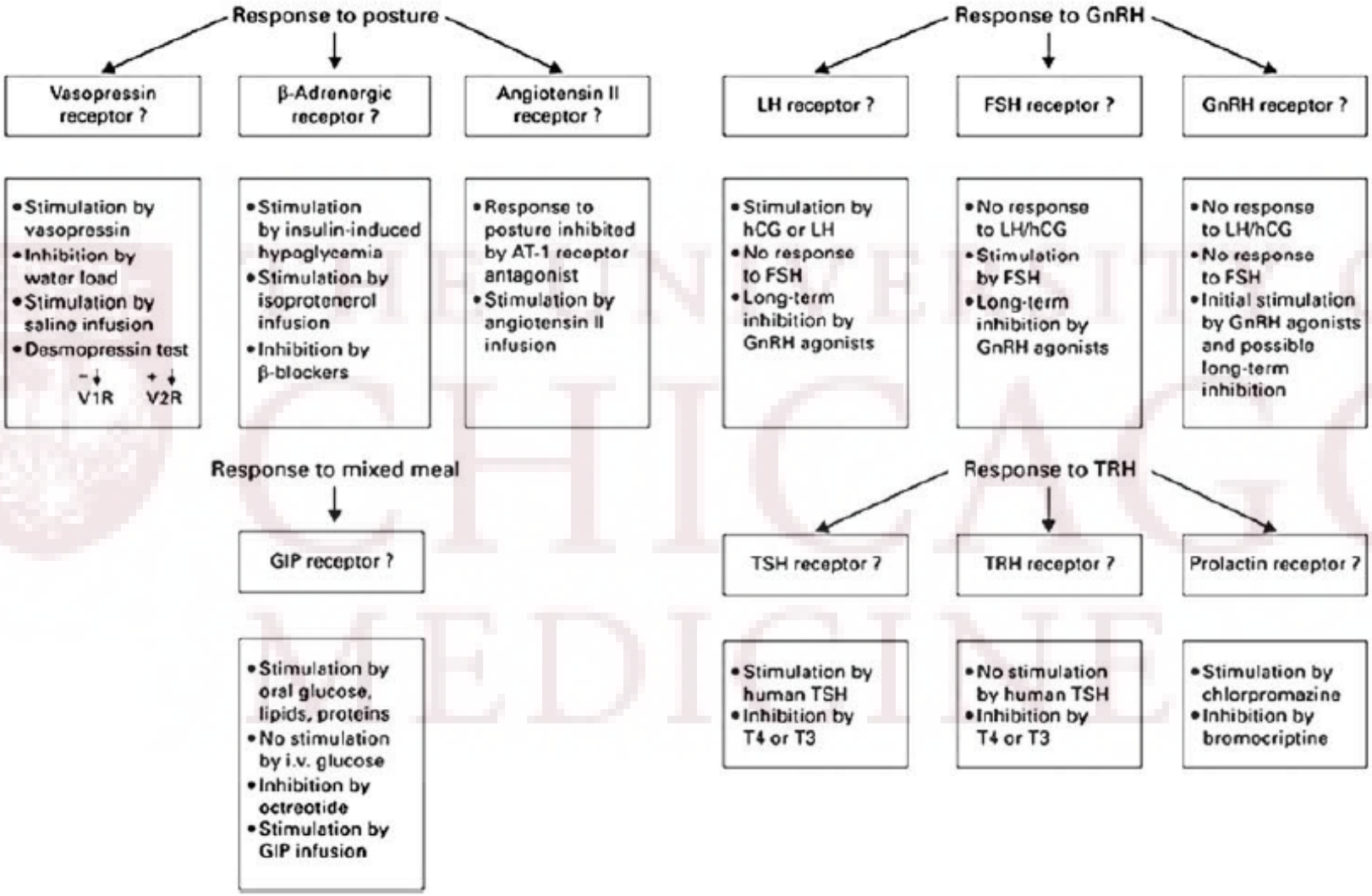
- Confirm Cushing`s syndrome
- ACTH-independent macronodular hyperplasia can be distinguished from ACTH-dependent macronodular hyperplasias by measuring plasma ACTH. Plasma ACTH is suppressed by excess cortisol in AIMAH (<5 pg/mL) and is inappropriately normal or slightly high in ACTH-dependent macronodular hyperplasia (≥15 pg/mL).
- Test for aberrant receptors

In-vivo screening protocol to detect the presence of aberrant adrenal hormone receptors in adrenal Cushing's syndrome.

Time (min)	Day 1	Day 2	Day 3
−60	Fasting supine	Fasting supine	Fasting supine
−15	[a]	[a]	[a]
0	Upright[a]	GnRH 100 μg i.v.[a]	Glucagon 1 mg i.v.[a]
+30	Upright[a]	[a]	[a]
+60	Upright[a]	[a]	[a]
+90	Upright[a]	[a]	[a]
+120	Upright[a]	[a]	[a]
+150	Supine[a]	(meal)	
+180	Mixed meal[a]		Vasopressin 10 IU i.m.
+210	[a]		[a]
+240	[a]		[a]
+270	[a]	[a]	[a]
+300	[a]	TRH 200 μg i.v.[a]	[a]
+330		[a]	
+360	ACTH 1–24 250 μg i.v.[a]	[a]	Metoclopramide 10 mg orally[a]
+390	[a]	[a]	[a]
+420	[a]	[a]	[a]
+450	[a]		[a]
+480	[a]		[a]

ACTH, adrenocorticotropic hormone; GnRH, gonadotrophin-releasing hormone; TRH, thyrotropin releasing hormone.
Modified from Lacroix et al (1999, *The Endocrinologist* **9:** 9–15) with permission.

[a] Blood samples for determination of cortisol, other hormones, and vital signs.


Response to posture
Vasopressin receptor ?
β-Adrenergic receptor ?
Angiotensin II receptor ?
• Stimulation by vasopressin
• Inhibition by water load
• Stimulation by saline infusion
• Desmopressin test
− ↓ V1R
+ ↓ V2R
• Stimulation by insulin-induced hypoglycemia
• Stimulation by isoprotenerol infusion
• Inhibition by β-blockers
• Response to posture inhibited by AT-1 receptor antagonist
• Stimulation by angiotensin II infusion
Response to GnRH
LH receptor ?
FSH receptor ?
GnRH receptor ?
• Stimulation by hCG or LH
• No response to FSH
• Long-term inhibition by GnRH agonists
• No response to LH/hCG
• Stimulation by FSH
• Long-term inhibition by GnRH agonists
• No response to LH/hCG
• No response to FSH
• Initial stimulation by GnRH agonists and possible long-term inhibition
Response to mixed meal
GIP receptor ?
• Stimulation by oral glucose, lipids, proteins
• No stimulation by i.v. glucose
• Inhibition by octreotide
• Stimulation by GIP infusion
Response to TRH
TSH receptor ?
TRH receptor ?
Prolactin receptor ?
• Stimulation by human TSH
• Inhibition by T4 or T3
• No stimulation by human TSH
• Inhibition by T4 or T3
• Stimulation by chlorpromazine
• Inhibition by bromocriptine

Treatment:

- Bilateral adrenalectomy
- In patients with moderately increased hormonal production, unilateral adrenalectomy has been proposed as a safe and effective alternative
- Pharmacological therapy: adrenal enzyme inhibitors are sometimes given to patients with overt Cushing's syndrome to control cortisol secretion before surgery

Pharmacological treatment in the presence of aberrant receptors:

- blockade of postprandial release of GIP with octreotide or pasireotide led to clinical and biochemical improvement of Cushing's syndrome, but did not persist in the long-term, probably because of eventual desensitization of somatostatin receptors in GIP-secreting duodenal K cells
- In catecholamine-dependent Cushing's syndrome, beta-adrenergic receptor antagonists (propranolol) were efficient in the long-term control of hypercortisolism
- In LH/hCG-dependent Cushing's syndrome, suppression of endogenous LH levels with long-acting leuprolide acetate controlled steroid secretion
- When specific receptor antagonists for vasopressin, serotonin, GIP, or other aberrant receptors become available, a broader range of pharmacological therapies could become useful

Take home points:

- Bilateral macronodular adrenal hyperplasia is a rare cause of Cushing syndrome, as it is estimated to represent less than 1% of endogenous cases
- The most prevalent abnormality results from the aberrant adrenal expression of ectopic or increased activity of eutopic peptide hormone receptors
- Patients should undergo screening for aberrant receptors, as this may change the therapeutic strategy

References:

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