Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline

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Task Force Members

Maria Fleseriu, MD

Ibrahim A. Hashim, PhD

Niki Karavitaki, PhD

Shlomo Melmed, MD

M. Hassan Murad, MD

Roberto Salvatori, MD

Mary H. Samuels, MD

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Contents

I. Introductory Case

II. Overview of *Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline*

III. Cases

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I. Introductory Case Question

A 32-year-old man with a history of a hypothalamic tumor treated with high-dose radiation therapy at age 26 years presents with symptoms of multiple anterior pituitary hormone deficits.

Which of the following is TRUE?

A. If he has GH deficiency and GH replacement is started, his other hormone replacement therapy may need to be adjusted.
B. Free T3 measurements are recommended for diagnosis and monitoring of central hypothyroidism.
C. Provocative testing to diagnosis central AI is always needed if the random AM serum cortisol is <3 mcg/dL (<83 nmol/L).
D. Provocative testing for GH deficiency is required in patients with three other proven hormone deficiencies.

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I. Introductory Case Answer

A 32-year-old man with a history of a hypothalamic tumor treated with high-dose radiation therapy at age 26 years presents with symptoms of multiple anterior pituitary hormone deficits.

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II.

Overview of *Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline*

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GRADE Classification of Guideline Recommendations

QUALITY OF EVIDENCE		High Quality	Moderate Quality	Low Quality	Very Low Quality
Description of Evidence		• *Well-performed RCTs* • *Very strong evidence from unbiased observational studies*	• *RCTs with some limitations* • *Strong evidence from unbiased observational studies*	• *RCTs with serious flaws* • *Some evidence from observational studies*	• *Unsystematic clinical observations* • *Very indirect evidence observational studies*
STRENGTH OF RECOMMENDATION	**Strong (1):** **"We recommend…"** *Benefits clearly outweigh harms and burdens, or vice versa*	1|⊕⊕⊕⊕	1|⊕⊕⊕O	1|⊕⊕OO	1|⊕OOO
	Conditional (2): **"We suggest…"** *Benefits closely balanced with harms and burdens*	2|⊕⊕⊕⊕	2|⊕⊕⊕O	2|⊕⊕OO	2|⊕OOO

DIAGNOSIS OF HYPOPITUITARISM
Central Adrenal Insufficiency (AI)

- We suggest performing a corticotropin stimulation test when morning cortisol values are between 3–15 mcg/dL to diagnose AI (2|⊕⊕◯◯)

- We suggest HPA biochemical testing at least 18–24 hours after the last HC dose or longer for synthetic glucocorticoids (GCs) (2|⊕⊕◯◯)

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DIAGNOSIS OF HYPOPITUITARISM
Central Hypothyroidism

- We recommend measuring serum free thyroxine (fT4) and TSH to evaluate central hypothyroidism (CH) (1|⊕⊕⊕⊕)
  - An fT4 level below the reference range in conjunction with a low, normal, or mildly elevated TSH in the setting of pituitary disease usually confirms CH
  - Depending on the clinical context, some patients with pituitary disease and low-normal fT4 levels may also have CH

- We suggest against using dynamic TSH-secretion testing to diagnose CH (2|⊕⊕⊕◯)

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DIAGNOSIS OF HYPOPITUITARISM
Growth Hormone Deficiency

- In patients with suspected GH deficiency (GHD), we recommend GH stimulation testing. Single GH measurements are not helpful. (1|⊕⊕⊕◯)
- We recommend using appropriately controlled body mass index (BMI) cut-offs to assess peak GH values. (1|⊕⊕◯◯)
- We suggest against biochemical testing for GHD in patients with clear-cut features and three other documented pituitary hormone deficits. (2|⊕⊕⊕◯)

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DIAGNOSIS OF HYPOPITUITARISM
Male Central Hypogonadism

- In males with suspected hypogonadism, we recommend measuring serum testosterone, FSH, and LH for diagnosis (1|⊕⊕◯◯)
- We recommend testing in the absence of acute/sub-acute illness and prior to 10:00 AM (following overnight fast) combined with serum PRL (1|⊕⊕◯◯)

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DIAGNOSIS OF HYPOPITUITARISM
Female Central Hypogonadism

- In the presence of oligomenorrhea or amenorrhea, we recommend measuring serum estradiol (E2), FSH, and LH. Other causes of menstrual irregularities and pregnancy should be excluded (1|⊕⊕◯◯)
- We suggest against dynamic testing with GnRH (2|⊕⊕◯◯)
- We recommend that in postmenopausal women, the absence of high serum FSH and LH are sufficient for diagnosing gonadotrope dysfunction if patient is not on hormonal replacement therapy. (1|⊕⊕⊕◯)

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DIAGNOSIS OF HYPOPITUITARISM
Central Diabetes Insipidus

- We recommend simultaneously measuring serum and urine osmolarity in patients with polyuria – more than 50 mL/kg body weight (e.g., 3.5 L/day in a 70 kg person) (1|⊕⊕⊕◯)
  - In the presence of high serum osmolarity (>295 mosmol/L), urine osmolarity should reach approximately 600 mosmol/L (urine /plasma osm ratio should be ≥2); while urine dipstick should be negative for glucose

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DIAGNOSIS OF HYPOPITUITARISM
Hormonal Assays

- Accurate and reliable measurements are central to diagnose hypopituitarism and monitoring therapies.
- Technical considerations:
  - Assay characteristics (sensitivity and reliability at low levels)
  - Sample stability
  - Interference from replacement hormonal therapies and their analogues (e.g., prednisolone, prednisone, and hydrocortisone in cortisol assays).

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MANAGEMENT OF HYPOPITUITARISM
Interactions between Replacement Hormones

Glucocorticoids and Growth Hormone

- We suggest testing HPA axis before and after starting GH replacement in patients not receiving GC replacement and with normal pituitary-adrenal function. (2|⊕◯◯◯)

Glucocorticoids and Thyroid Hormone

- We suggest evaluating patients with CH for AI prior to starting L-T4 therapy.
  - If this is not feasible, empiric GC should be prescribed in patients starting L-T4 therapy until there is a definitive evaluation for AI (2|⊕⊕◯◯)

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MANAGEMENT OF HYPOPITUITARISM
Interactions between Replacement Hormones

Estrogen and Thyroid Hormones

- In patients with CH requiring changes in estrogen therapy, we recommend monitoring fT4 levels and adjusting L-T4 doses to maintain fT4 levels within target ranges (1|⊕⊕⊕◯)

Growth Hormone and Estrogen

- We suggest that women on oral estrogen replacement receive higher GH doses compared with eugonadal females or males. (2|⊕⊕⊕◯)

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MANAGEMENT OF HYPOPITUITARISM
Interactions between Replacement Hormones

Glucocorticoids and Diabetes Insipidus

- Because AI may mask the presence of partial DI, we suggest monitoring for the development of DI after starting GC replacement. Conversely, patients with improved DI without an AI diagnosis should undergo AI testing. (2|⊕○○○)

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MANAGEMENT OF HYPOPITUITARISM
Pituitary Surgery

- In patients with AI, we recommend GC stress doses before surgery and tapered doses after awaiting repeating testing (1|⊕⊕⊕◯)

- In patients with normal preoperative adrenal function, we suggest an individualized clinical approach for postoperative GC administration until the HPA axis can be evaluated (2|⊕⊕◯◯)

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MANAGEMENT OF HYPOPITUITARISM
Pituitary Surgery

- With preoperative central hypothyroidism (CH), we recommend using L-T4 before non-emergency surgery and throughout the perioperative period (1|⊕⊕⊕◯)
- With intact preoperative thyroid function, we recommend measuring fT4 levels 6-8 weeks post-operatively to assess for CH. (1|⊕⊕◯◯)

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MANAGEMENT OF HYPOPITUITARISM
Pituitary Surgery

- We suggest that initial therapy for DI utilizes short-acting subcutaneous aqueous ADH, allowing for safer use in the vast majority of cases in whom DI resolves spontaneously. (2|⊕⊕◯◯)

- We do not suggest pre-scheduled DDAVP dosages in the first week post-surgery (2|⊕◯◯◯)

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MANAGEMENT OF HYPOPITUITARISM
Pituitary Surgery

- We suggest oral or intranasal DDAVP after discharge with clear instructions to use only if significant polyuria occurs (2|⊕◯◯◯)
- We suggest retesting all pituitary axes 6 weeks after pituitary surgery and then periodically to monitor development or resolution of pituitary deficiencies (2|⊕⊕◯◯)

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MANAGEMENT OF HYPOPITUITARISM
Pituitary Apoplexy

- We recommend testing for acute pituitary insufficiency in all patients with pituitary apoplexy (1|⊕⊕⊕◯)
- As acute adrenal insufficiency (AI) is a major cause of mortality, we recommend GC therapy until a laboratory diagnosis is established and the patient maintains normal pituitary function (1|⊕⊕◯◯)

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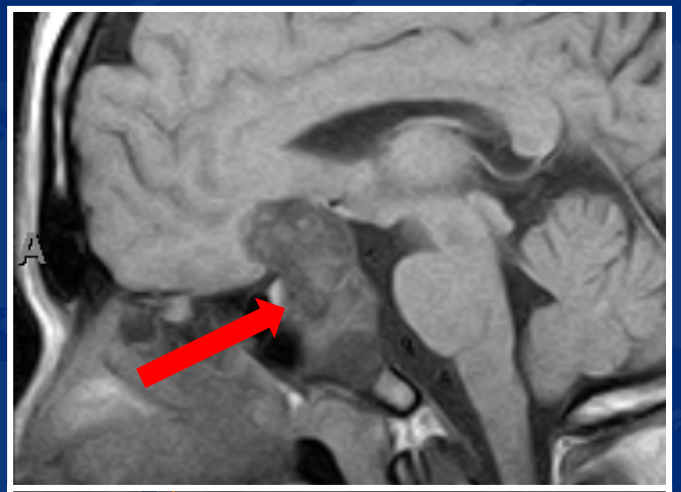
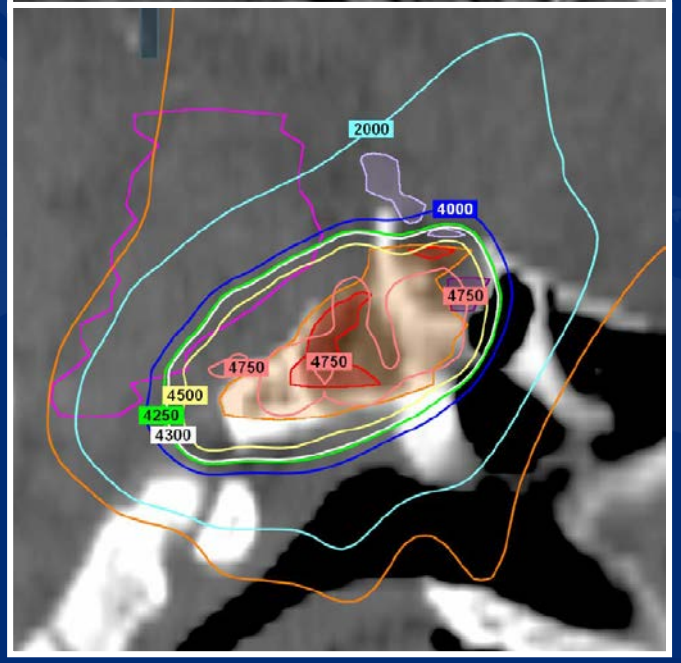
III. Cases

Case #1: Risk Assessment

- 22-year-old male with a clival chordoma

- Treatment was just completed and included:
  - Surgery
  - Proton radiotherapy
    45 ^{60}Co-Gy equivalents *plus*
    25.2 ^{60}Co-Gy boost to clivus





Question

Which of the following statements is TRUE?

A. He is at low-moderate risk for hypopituitarism.
B. If he does not already have established diabetes insipidus, he is not likely to get DI in the future.
C. He should undergo annual provocative stimulation testing to screen for hypopituitarism.
D. He should be counseled that he will never be able to father a child.
E. None of the above.

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Answer

Which of the following statements is TRUE?

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B. If he does not already have established diabetes insipidus, he is not likely to get DI in the future.
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D. He should be counseled that he will never be able to father a child.
E. None of the above.

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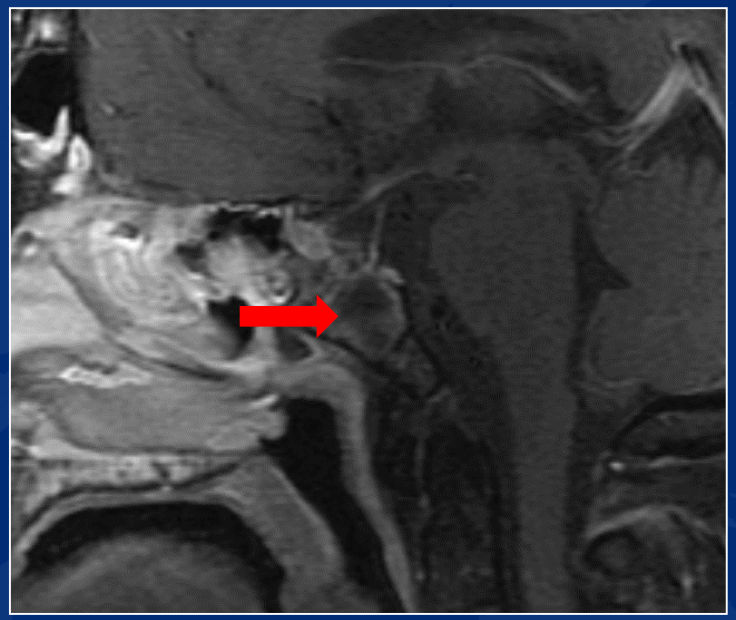
Case #1: Continued

- Despite being advised to have annual endocrine evaluations, patient lost to FU for 5 years
- He marries and is concerned because he has sexual dysfunction
- He also complains of fatigue but is otherwise without concerns
- MRI shows stable clival chordoma



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Case #1: Hormonal Evaluation

	Baseline 7/19/2007	Current 11/28/2012	Reference Range
ACTH	42	18	<46 pg/mL
Cortisol	13.1	2.1	4.3–22.4 ug/dL
TSH	3.1	3.02	0.5–5.5 mIU/L
Free T4	0.9	0.61	0.9–1.8 ng/dL
LH	6.4	0.7	1.7–11.2 mIU/mL
FSH	2	ND	1.0–42 mIU/mL
Testosterone	320	<20	241–827 ng/dL
IGF-1	193	52	126–382 ng/mL
Prolactin	19.3	22.3	3.3–20.8 ng/mL

Question

How should the patient be counseled now?

A. He will need provocative testing for all axes to confirm hypopituitarism.

B. He should start levothyroxine before starting GC therapy to improve his fatigue.

C. Glucocorticoid replacement should be initiated before thyroid hormone initiation.

D. He would never be a candidate for GH therapy.

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Answer

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D. He would never be a candidate for GH therapy.

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Case #2: Treatment

A 32-year-old woman with a history of clinically non-functional macroadenoma status post surgery with panhypopituitarism presents to discuss possible pregnancy within the next year.

- Current medications:
  - Hydrocortisone 20 mg daily
  - Levothyroxine 75 mcg daily
  - Desmopressin 0.1 mg BID
  - Estrogen patch with monthly progesterone
  - rhGH 0.6 mg daily

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Question

Which of the following actions should be taken?

A. Change her GC regimen to prednisone to prepare her for pregnancy.

B. Increase hydrocortisone from 20 mg to 30 mg daily pre-pregnancy.

C. Increase levothyroxine to 100 mcg daily and recheck TSH in the first 3-4 weeks after she gets pregnant.

D. Advise patient that she will need to continue DDAVP in pregnancy and might require higher daily doses.

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Answer

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D. Advise patient that she will need to continue DDAVP in pregnancy and might require higher daily doses.

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MANAGEMENT OF HYPOPITUITARISM
In Pregnancy

Thyroid

- We recommend that clinicians monitor fT4 or total T4 levels every 4-6 weeks for women with CH who become pregnant, and that these women may require increased L-T4 doses to maintain levels within target ranges for pregnancy (1|⊕⊕◯◯)

DDAVP

- In pregnant women with pre-existing DI, we suggest continuing DDAVP during pregnancy and adjusting doses if required (2|⊕⊕◯◯)

Growth Hormone

- We suggest discontinuing GH replacement during pregnancy, as there is no clear evidence yet for efficacy or safety, and the placenta produces GH (2|⊕⊕◯◯)

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MANAGEMENT OF HYPOPITUITARISM
In Pregnancy

Adrenal

- Hydrocortisone is the preferred physiologic GC replacement in pregnancy; it is degraded by the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) and does not cross the placenta.
- We suggest using a replacement dose of 12–15 mg/m^2 with adjustments based on clinical judgment.
- During labor and vaginal delivery, a stress dose of GC (50 mg IV hydrocortisone in the second stage of labor) should be administered.

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Case #3

A 73-yo man developed a sudden frontal headache with visual changes and was found to have a sellar mass. He was started on hydrocortisone, levothyroxine and testosterone replacement. He reports a 3-year history of fatigue, cold intolerance, and low libido. He is significantly feeling better since starting hormone replacement but he complains of double vision.

On physical examination his visual fields are normal but he has a left VI nerve palsy.

- Current medications:
  - Levothyroxine 75 mcg
  - Hydrocortisone 15 mg in AM and 5 mg in the PM
  - Testosterone gel 5 grams daily

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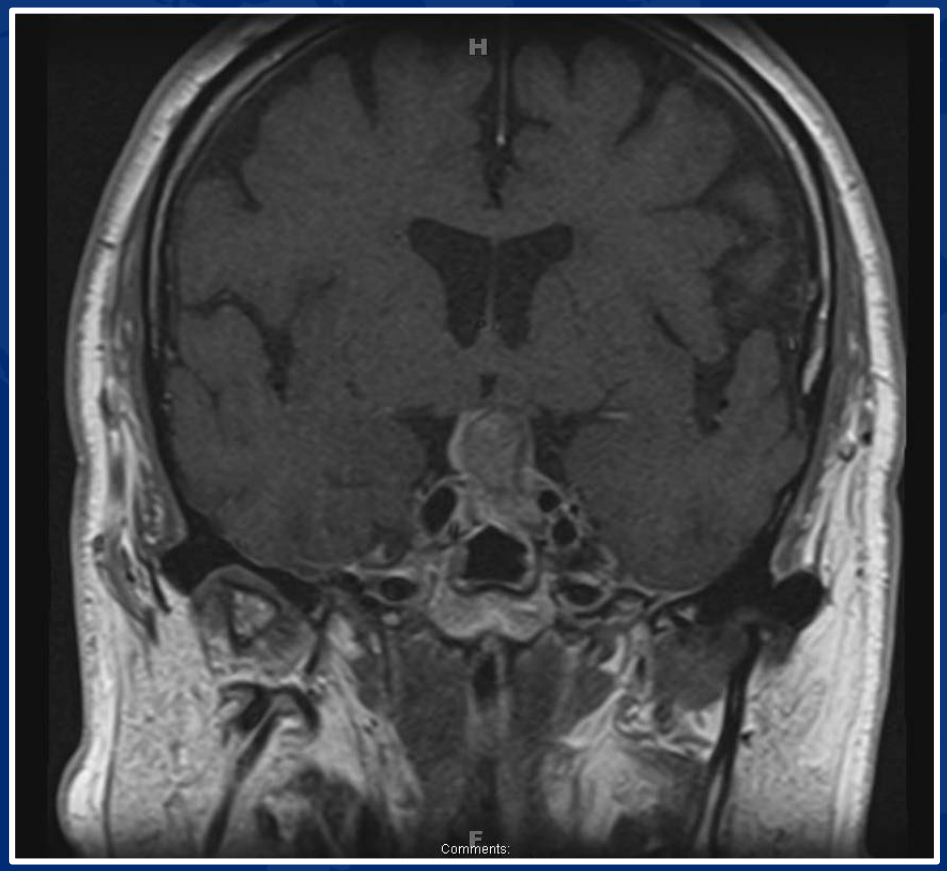
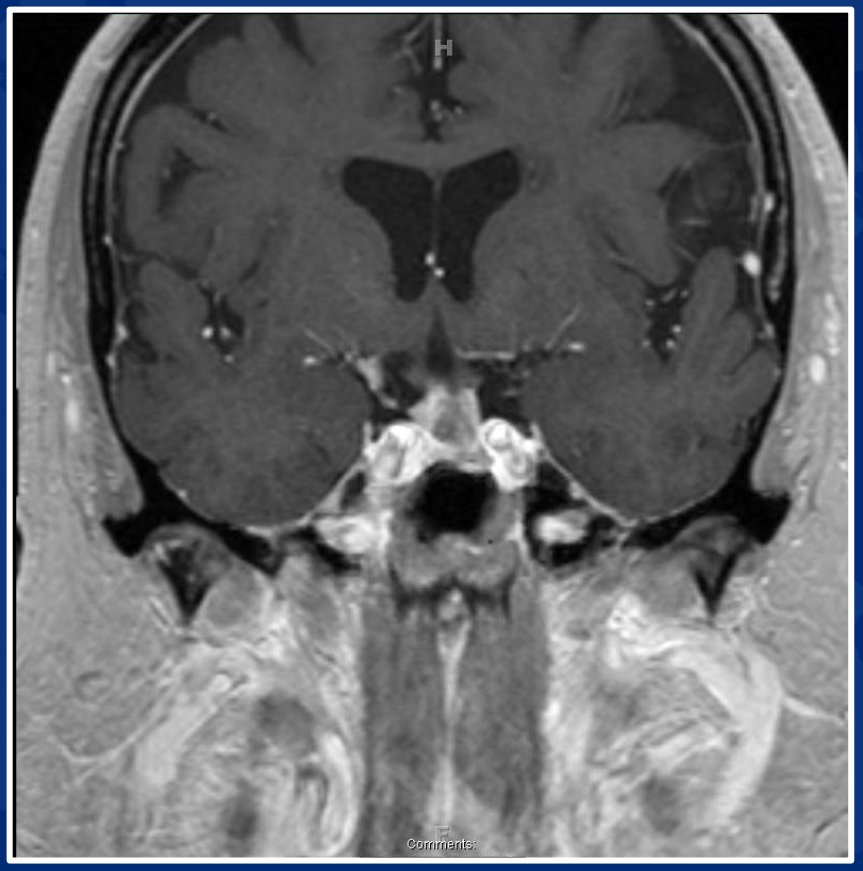
Case #3: Imaging

At Presentation



Two weeks later



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Case #3: Current Labs

	Current	Reference Range
Diluted PRL	10.1 ng/mL	3.0–14.7 ng/mL
Testosterone	160 ng/dL	160–726 ng/mL
AM Cortisol	5.9 mcg/dL	6–26 mcg/dL
TSH	0.3mIU/mL	0.50–4.50 mIU/mL
Free T4	1.1 ng/dL	0.8–1.8 ng/dL
IGF-1	44 ng/mL	34–245 ng/mL

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Case #3: Follow-up

- Cosyntropin stim. test 3 months later abnormal (peak cortisol 11 mcg/dL)
- Instructions on stress steroid management and use of medical alert bracelet re-emphasized with patient
- Continued hydrocortisone (15 mg in AM and 5 mg in PM), levothyroxine (75 mcg/day), and testosterone gel
- 3 months later: he fell and hit his head; due to possible seizure activity, started on phenytoin
- 3 months later: he reports normal libido, normal appetite (no weight loss), and worsening fatigue
- Labs:

	Current	Reference Range
Testosterone	250 ng/dL	160–726 ng/mL
Free T4	0.6 ng/dL	0.8–1.8 ng/dL
IGF-1	45 ng/mL	34–245 ng/mL

Question

Which of the following would most likely address his current complaints?

A. Starting growth hormone replacement after additional provocative testing
B. Increasing the levothyroxine dose
C. Starting fludrocortisone
D. Increasing the testosterone dose to get the testosterone level in the mid-normal range

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Answer

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MANAGEMENT OF HYPOPITUITARISM
In Patients Receiving Antiepileptic Medications

Central Hypothyroidism

- In CH patients receiving L-T4, we recommend checking fT4 at least 6 weeks after starting AED, and increasing L-T4 doses if fT4 levels decrease below the target range (1|⊕⊕◯◯)

Adrenal Insufficiency

- We suggest clinicians educate AI patients that are taking non-dexamethasone GCs and who start enzyme inducing antiepileptic drugs (AEDs) about the early signs and symptoms of AI (2|⊕⊕◯◯)
- In patients with AI on dexamethasone, we suggest increasing dexamethasone replacement doses if enzyme-induced AEDs are co-administered (2|⊕◯◯◯)

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