Pituitary Board Review
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1. A 31-year-old woman with a history of prolactinoma is now in her 37th week of pregnancy. Two years ago, a 14-mm prolactinoma was identified. Her initial prolactin level was 320 ng/mL (13.9 nmol/L) (reference range, 4-30 ng/mL [0.17-1.30 nmol/L]), and there was suprasellar extension on MRI, chiasmal compression, and a small visual field defect. With cabergoline, 0.5 mg twice weekly, her prolactin normalized, her galactorrhea and amenorrhea resolved, her visual field normalized, and her tumor decreased in size to 5 mm. She stopped cabergoline when she learned she was pregnant. She now reports increasing headaches that are quite severe. Goldmann visual field testing is normal.

Question 1 (1/1)

Which of the following is the best next step in her management?
A. Restart the cabergoline now 14%
B. Deliver the baby 25%
C. Proceed with transphenoidal surgical tumor removal 1%
D. Perform a pituitary-directed MRI 57%
E. Perform a pituitary-directed CT 3%

Question 1

2. A 39-year-old man presents with decreased libido and erectile dysfunction and is found to have a prolactin level of 49 ng/mL (2.1 nmol/L) (reference range, 4-23 ng/mL [0.17-1.00 nmol/L]) and a 13-mm pituitary adenoma on MRI. His testosterone concentration is 275 ng/dL (9.5 nmol/L). His prolactin level, libido, and erectile function normalize on cabergoline, 0.5 mg weekly, and he has remained on this treatment for 2 years. Over the past few months, he has developed headaches. His physical examination shows normal virilization and all other findings are normal as well.

Question 2 (1/1)

Effect of Pregnancy on Prolactinomas

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Previous Therapy</th>
<th>No. Pts</th>
<th>No. Pts With Tumor Enlargement</th>
</tr>
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<tbody>
<tr>
<td>Microadenomas</td>
<td>None</td>
<td>658</td>
<td>18 (2.7%)</td>
</tr>
<tr>
<td>Macroadenomas</td>
<td>None</td>
<td>214</td>
<td>49 (22.9%)</td>
</tr>
<tr>
<td>Macroadenomas</td>
<td>Surgery/XRT</td>
<td>148</td>
<td>7 (4.8%)</td>
</tr>
</tbody>
</table>


Which of the following should be the next management step?
A. Stop the cabergoline 5%
B. Perform a pituitary-directed MRI 91%
C. Perform an echocardiogram 1%
D. Switch the cabergoline to testosterone 0%
E. Switch the cabergoline to bromocriptine 3%

Question 2
39-Year-Old Man With Mild Hyperprolactinemia and 13-mm Adenoma 3 Years Ago

Beware of a discordance between the PRL level and the size of the tumor. The PRL may come down with a dopamine agonist but the nonfunctioning adenoma may still be increasing in size.

Not 11 mm anymore

3. Acromegaly is diagnosed in a 63-year-old woman. Her initial MRI showed a 1.3-cm pituitary tumor with minimal extension superiorly and laterally. After transsphenoidal surgery, she still has some residual tumor in the left cavernous sinus. Her postoperative GH level is 3.0 ng/mL (3.0 µg/L) and it does not suppress with hyperglycemia after a glucose load. Her IGF-1 level is 290 ng/mL (38.0 nmol/L) (reference range, 72-207 ng/mL [9.4-27.1 nmol/L]).

Question 3 (1/1)

Which of the following treatment options would you recommend now?

A. Gamma-knife irradiation of the residual tumor 16%
B. Lanreotide weekly for 4 weeks, then depot monthly 55%
C. Cabergoline, twice weekly 13%
D. Another transsphenoidal surgery 3%
E. Pegvisomant, once weekly 13%

Question 3

Effects of Adjunctive Therapy With Cabergoline Following Surgery and/or Irradiation on IGF-1 Levels in Patients With Acromegaly

<table>
<thead>
<tr>
<th>Series</th>
<th>No.</th>
<th>% with Normal IGF-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colao (1997)</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Abs (1998)</td>
<td>64</td>
<td>39</td>
</tr>
<tr>
<td>Cozzi (1998)</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>Moyes (2008)</td>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td>TOTAL</td>
<td>108</td>
<td>32</td>
</tr>
</tbody>
</table>

4. A 57-year-old woman with acromegaly has a GH level of 11.7 ng/mL (11.7 µg/L) and an IGF-1 level of 631 ng/mL (82.7 nmol/L) (reference range, 78-220 ng/mL [10.2-28.8 nmol/L]) after surgery. As one of the complications of acromegaly, she has difficult-to-control diabetes mellitus (hemoglobin A1c level, 8.4% [0.084]). She is very concerned about the type of adjunctive medical therapy she should have.

Question 4 (1/1)

Which of the following medications is most likely to worsen her diabetes control?

A. Octreotide LAR 39%
B. Lanreotide depot 5%
C. Pegvisomant 17%
D. Cabergoline 2%
E. Pasireotide 38%

Question 4
Worsening of Glucose Tolerance with Pasireotide in Acromegaly
Prospective Randomized Study Comparing Pasireotide to Lanreotide

- Change in Hemoglobin A1c levels:
  - Diabetic pts: Pasireotide +0.87% vs Lanreotide +0.03%
  - Prediabetic pts: Pasireotide +0.64% vs Lanreotide +0.11%
  - Nondiabetic pts: Pasireotide +0.75% vs Lanreotide +0.37%

- Antidiabetic medication required:
  - Pasireotide: 44.4%
  - Lanreotide: 26.1%


5. An 18-year-old girl develops severe headaches. Head MRI shows a cystic sellar and suprasellar mass with calcifications. In retrospect, she has been tired, and her menses, which began at age 12 years, stopped 1 year ago. On physical examination, her vision is normal, as are the rest of the examination findings.

Laboratory test results:
- Free T4 = 0.9 ng/dL (11.6 pmol/L)
- Cortisol (8 AM) = 7.1 μg/dL (195.9 nmol/L)
- Estradiol = 22 pg/mL (80.8 pmol/L)
- Prolactin = 355 ng/mL (15.4 nmol/L)
- IGF-1 = 122 ng/mL (16.0 nmol/L)

On the basis of the presented information, which of the following treatments should you recommend?

- A. Dopamine agonist 46%
- B. Transcranial surgery 15%
- C. Transsphenoidal surgery 35%
- D. Supervoltage radiation 1%
- E. Gamma-knife irradiation 3%

Do the Limits of Serum Prolactin in Disconnection Hyperprolactinemia Need Re-definition?

6. A 34-year-old woman has developed florid features of Cushing syndrome during her second month of pregnancy. She has developed hypertension, diabetes mellitus, hirsutism; and wide, purple striae on her abdomen.

Laboratory test results:
- Serum cortisol (8 AM) = 37 μg/dL (1020.8 nmol/L)
- ACTH = 129 pg/mL (28.4 pmol/L) (reference range, 10-60 pg/mL [2.2-13.2 pmol/L])
- Urinary free cortisol = 475 μg/24 h (1311 nmol/d) (reference range, 4-50 μg/24 h [11-138 nmol/d])

MRI shows a 6-mm pituitary adenoma.

Question 6 (1/1)

Which of the following treatment options is most likely to have a successful outcome?

A. Ketoconazole  
B. Transsphenoidal surgery  
C. Mifepristone  
D. Pasireotide  
E. Cabergoline

4%  
84%  
5%  
4%  
4%

Cushing Disease
Primary Treatment is Transsphenoidal Surgery

Ivan Ciric learned the technique using the operating microscope from Jules Hardy in Montreal and was the first to perform transsphenoidal surgery using this technique in the US.

Of 136 patients operated by Dr. Ciric, the overall immediate postop remission rate was 83.4% and 89.8% for microadenomas - 9.7% risk of recurrence after mean of 68.5 months


Summary: Drugs for Cushing Disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cushing Disease Only?</th>
<th>Normal UFC</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metyrapone</td>
<td>N</td>
<td>26%</td>
<td>Nausea, hirsutism, ↑BP</td>
</tr>
<tr>
<td>Mitotane</td>
<td>N</td>
<td>57%</td>
<td>GI, Neurologic</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>N</td>
<td>49%</td>
<td>↑LFT, Liver failure</td>
</tr>
<tr>
<td>Etopitrate</td>
<td>N</td>
<td>100%</td>
<td>IV only, ICU needed, sedation</td>
</tr>
<tr>
<td>Cabergoline</td>
<td>Y</td>
<td>37%</td>
<td>Nausea</td>
</tr>
<tr>
<td>Mifepristone</td>
<td>N</td>
<td>NA*</td>
<td>Adrenal insufficiency, hypokalemia, menorrhagia</td>
</tr>
<tr>
<td>Pasireotide</td>
<td>Y</td>
<td>26%</td>
<td>Hyperglycemia, other SRL adverse effects</td>
</tr>
<tr>
<td>LC1699</td>
<td>N</td>
<td>80%</td>
<td>Hypokalemia</td>
</tr>
</tbody>
</table>

*Cortisol and ACTH measurements not reflective of biologic activity.
22/25 (88%) with diabetes had at least 25% reduction in Glucose AUC during OGGT.

7. A 77-year-old woman is found to have hyperthyroidism with a large, multinodular goiter when she presents with increasing angina. Atrial fibrillation and heart failure are diagnosed.

Laboratory test results:
- Free T₄ = 2.8 ng/dL (36.0 pmol/L) (reference range, 0.8-1.8 ng/dL [10.3-23.2 pmol/L])
- Total T₃ = 413 ng/dL (6.4 nmol/L) (normal)
- TSH = 1.9 mU/L (reference range, 0.5-5.0 mIU/L)

She has a history of extensive coronary artery disease. A radioiodine scan shows a 1.3-cm, nonfunctioning thyroid nodule, and FNAB documents papillary thyroid cancer. MRI reveals a 2.1-cm pituitary adenoma invading the cavernous sinus.

Question 7 (1/2)

Question 7 (2/2)
Which of the following treatments should be administered next?
A. Cabergoline  9%
B. Saturated solution of potassium iodide  27%
C. Radioactive iodine  4%
D. Lanreotide depot  22%
E. Subtotal thyroidectomy  38%

Treatment of TSH-omas with Octreotide and Lanreotide (n = 103)
- TSH reduced to <50% basal  90%
- α-subunit reduction  93%
- TSH & α-subunit normalization  75%
- T₄/T₃ normalization  96%
- Goiter reduction  20%
- Vision improvement  75%
- Tumor shrinkage  45%
- True escape  10%
- Resistance  4%
- D/C of therapy due to side effects  7%

8. A 28-year-old woman has had amenorrhea for 4 years and is found to have a serum prolactin level of 48.3 ng/mL (2.1 nmol/L). Evaluation documents normal thyroid, renal, and hepatic function and a negative pregnancy test. MRI reveals a 4-mm hypointense area in the pituitary compatible with a microadenoma. Although she is sexually active, she is not planning to get pregnant for at least 4 to 5 years. She has poor health insurance and is concerned about the cost of medications.

Which of the following is the best treatment plan for this woman?
A. Transsphenoidal surgery  1%
B. Bromocriptine  28%
C. Cabergoline  9%
D. Oral contraceptives  50%
E. Reassurance  12%

9. Cushing disease is diagnosed in a 48-year-old woman. Her preoperative morning cortisol level is 26.7 μg/dL (736.6 nmol/L), and her morning ACTH level is 109 pg/mL (24.0 pmol/L) [reference range, 10-60 pg/mL (2.2-13.2 pmol/L)]. MRI shows a 4-mm lesion. Twenty-four hours after transsphenoidal surgery, her morning cortisol level is 11 μg/dL (303.5 nmol/L) and she is to be discharged home.

Which of the following should you tell this patient?
A. She should consider having another transsphenoidal operation performed by an experienced pituitary surgeon  15%
B. She will need to take maintenance hydrocortisone daily, as well as stress dosing for close to a year  25%
C. She should be started on medical therapy for persistent Cushing disease  13%
D. She should be referred for gamma-knife stereotactic radiotherapy  5%
E. She should have an ACTH stimulation test to determine whether maintenance hydrocortisone treatment is needed  42%
Should We Re-operate?

- Role of early re-operation for persistent disease
  - Re-operation 7-46 days postoperatively
  - 12/17 (71%) resolution of hypercortisolism
- Increased risk of hypopituitarism
  - 5% if selective adenomectomy
  - 50% if aggressive resection


10. A 26-year-old woman is found to have lymphoma involving her hypothalamus after she presents with polyuria and polydipsia. On further evaluation, panhypopituitarism, complete diabetes insipidus, and a markedly impaired thirst mechanism are diagnosed. While on anterior pituitary hormone replacement and twice-daily DDAVP, a serum sodium concentration of 116 mEq/L (116 mmol/L) is documented. Her blood pressure is 124/68 mm Hg, her pulse rate is 76 beats/min, her skin is “doughy,” and she is very confused.

Which of the following is the best treatment plan?

A. Hold DDAVP, restrict fluid intake to 1000 mL, and check serum sodium in 12 hours 4%
B. Hold DDAVP, restrict fluid intake to 1000 mL, and check serum sodium every 2 to 4 hours 40%
C. Hold DDAVP, but give hypertonic saline to raise the serum sodium by 6 mEq/L (6 mmol/L) over 6 hours 45%
D. Give DDAVP and give normal saline 4%
E. Give DDAVP and give hypertonic saline 7%

Clinical Course of Patients with Severe Hyponatremia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Clinical course</th>
<th>Brain Lesions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Treatment</td>
<td>Respiratory Arrest</td>
<td>Cerebral Edema</td>
<td>Death: Brain Damage</td>
</tr>
<tr>
<td>Na &gt;25 mEq in 24 h</td>
<td>Delayed Damage</td>
<td>Myelinolysis</td>
<td>Death: Brain Damage</td>
</tr>
<tr>
<td>Overcorrection</td>
<td>Respiratory Arrest</td>
<td>Myelinolysis</td>
<td>Death</td>
</tr>
<tr>
<td>Slow Correction</td>
<td>Do well</td>
<td>Normal Brain</td>
<td>No sequelae</td>
</tr>
</tbody>
</table>

11. A 33-year-old woman who is 31 weeks’ pregnant is concerned about hand and leg swelling and possible coarsening of her facial features. Her obstetrician refers her for evaluation for acromegaly after documenting a modestly elevated IGF-1 level.

Which of the following should be the next step?

A. Pituitary-directed MRI 4%
B. Repeated measurement of IGF-1 10%
C. Measurement of GH response during an oral glucose tolerance test 26%
D. Deferral of further workup until after delivery 61%
E. Use of octreotide long-acting release until after delivery 0%
12. A 37-year-old woman has been treated for a prolactinoma. Her prolactin level was initially 1593 ng/mL (69.3 nmol/L), and a 2.6-cm macroadenoma was visible on MRI. She responded well to cabergoline, 0.5 mg twice weekly, with an initial normalization of her prolactin level and shrinkage of her tumor to about 7 mm in height. However, 18 months later, her prolactin concentration has now increased to 284 ng/mL (12.3 nmol/L). On MRI, her tumor has grown again to 1.4 cm. She says she has been taking her medication regularly. She has not had any menses for a few months. Her cabergoline dosage is gradually increased, initially to 1 mg twice weekly and subsequently to 2 mg daily over the next year.

Question 12 (1/2)

However, her prolactin level continues to rise to 4513 ng/mL (196.2 nmol/L) and her tumor grows to 3.2 cm. The patient is adherent to her medication regimen and attends her clinic appointments. She subsequently undergoes a 2-stage transsphenoidal/transcranial near-total resection. However, the tumor regrows rapidly even on cabergoline, and she undergoes gamma-knife radiotherapy. Over the ensuing 2 years, the tumor has continued to grow and she is losing vision.

Question 12 (2/2)

Which of the following treatments is the best choice now?

A. Conventional radiotherapy  13%
B. Repeat craniotomy   20%
C. Temozolomide  45%
D. Ipilimumab  6%
E. Lanreotide  17%

Question 12

Malignant Prolactinoma

Definitions

- Macroadenoma
- Invasive macroadenoma
- Malignant prolactinoma (carcinoma)
  - Requires metastatic disease
    - Intracranial
    - Spinal
    - Extra CNS
Malignant Prolactinoma

Clinical Presentations

- Loss of responsivity to dopamine agonist in a previously responsive tumor
- Rapid regrowth after surgery
- Repeated operations for tumor growth and increase in prolactin levels
- Development of metastases


Malignant Prolactinoma Clinical Presentations

Temozolomide

- Temozolomide is an alkylating compound that depletes MGMT (O-6-methylguanine-DNA methyltransferase), a DNA repair enzyme that methylates DNA and exerts an antineoplastic effect
- Alkylating drugs not cell cycle-specific & can inhibit all stages of tumor-cell growth; therefore, patients with slow-growing tumors might be well suited to this drug type
- Absorbed rapidly after oral administration
- Readily crosses the blood-brain barrier
- Used for gliomas and cerebral metastases of melanoma
- Adverse effects: nausea, vomiting, fatigue, edema, myelosuppression, diffuse organizing pneumonitis (1 case)
- PCP also reported and prophylaxis recommended


13. An 18-year-old girl had a craniopharyngioma resected at age 15 years with resultant panhypopituitarism. She has been treated with levothyroxine, hydrocortisone, and GH. An oral contraceptive for estrogen and progesterone replacement was recently started. Over the past year, she has only grown 1 cm and her height is now is 64 in (162.6 cm). A recent hand and wrist film shows almost complete epiphyseal closure. After 1 month off GH therapy, her IGF-1 concentration is –2.7 standard deviations.

Question 13 (1/1)

If she does not continue GH treatment, which of the following is most likely?

A. Progressive mental deterioration 1%
B. Decreased peak bone mass 64%
C. Increased mortality rate 8%
D. Markedly decreased energy levels 25%
E. Amenorrhea 2%

Question 13

Changes in Total Bone Mineral Content and Density at 6 and 12 Months in GH-Deficient Adolescents Continuing or Discontinuing GH Therapy

14. A 24-year-old man presented with galactorrhea and failure to complete puberty at age 17 years. Initially his prolactin concentration was 16,150 ng/mL (702.2 nmol/L) and a pituitary MRI revealed a 2.3 3.4-cm hypodense sellar mass. Cabergoline was initiated, and the dosage was increased over several months. His prolactin level normalized and puberty resumed while on a cabergoline dosage of 2.5 mg twice weekly. Follow-up MRIs demonstrated a gradual reduction in tumor size. The most recent MRI 1 year ago showed some residual tumor in the floor of the sella. Over the past few visits, his prolactin measurements have been 1.4 ng/mL (0.06 nmol/L), 0.7 ng/mL (0.03 nmol/L), and 0.9 ng/mL (0.04 nmol/L).

Which of the following steps should be undertaken now?

A. Continue cabergoline at the present dosage until the tumor is no longer visible
B. Reduce the weekly cabergoline dosage by 0.5 mg every 4 to 8 weeks and monitor by measuring prolactin levels after each dose reduction
C. Discontinue cabergoline and start testosterone therapy
D. Discontinue cabergoline and schedule a pituitary MRI in 6 weeks
E. Refer for gamma-knife radiotherapy

15. A 34-year-old woman reports that she has decreased libido, and her primary care physician subsequently documents a prolactin level of 37 ng/mL (1.6 nmol/L). Her physician re-measures the prolactin (which is 45 ng/mL [2.0 nmol/L]) and orders further laboratory tests. The patient has a normal chemistry metabolic profile and a TSH level of 1.1 mIU/L. Her menses have been regular, and she has not noticed any galactorrhea. She was able to conceive without problems about 18 months ago and the pregnancy and delivery were without incident. She breastfed the baby for 2 to 3 months and did not have persistent galactorrhea. She is otherwise well except for some postpartum depression. Her examination findings are normal, with no goiter or expressible galactorrhea.

Circulating Forms of Prolactin

- Monomeric Prolactin – 23 kDa
- Glycosylated forms – 25 kDa with reduced biological activity
- Big Prolactin – 50kDa (dimers)
- Big. Big Prolactin (macroprolactin)
  - Most is bound to IgG (24%-86% of macroprolactin, depending upon method)
  - Some may be heteromers (14%-76%)
  - Less bioactive than monomeric
Macroprolactinemia

- Don’t measure PRL unless patient is symptomatic
- If symptoms equivocal and PRL levels elevated, consider assessing for macroprolactin (PEG precipitation)
  - Since about 30% of PRL can be precipitated by PEG in normals, the "normal" monomeric prolactin level is about 0.7 x normal range
  - Therefore, in given patient, the "monomeric" prolactin should still be judged against the normal monomeric range and if above that, patient should be considered to be hyperprolactinemic.
- If monomeric PRL elevated (see above) and/or patient is symptomatic (amenorrhea/galactorrhea), exclude other causes (TSH, creatinine) and do MRI
- If patient symptomatic, do therapeutic trial with dopamine agonist

Which of the following would be the best management strategy now?

A. Switch to octreotide LAR 6%
B. Switch to pegvisomant 12%
C. Add cabergoline 45%
D. Add pegvisomant once weekly and reduce the lanreotide dosage 31%
E. Refer for transsphenoidal surgery 6%

Benefits of Adding Cabergoline to Somatostatin Analogues

- IGF-1 percent change during SA + CAB compared with SA alone
- Patients are ranked by PRL level shown on the x-axis

16. A 69-year-old woman with acromegaly has a tumor partially wrapped around her right carotid artery, and she also has severe coronary artery disease. She elects to try lanreotide depot, and her GH and IGF-1 levels decrease to 3.9 ng/mL (3.9 µg/L) and 384 ng/mL (50.3 nmol/L) (reference range, 67-195 ng/mL [8.8-25.5 nmol/L]), respectively, while on a dosage of 120 mg once monthly. MRI shows a slight decrease in tumor size.

17. A 19-year-old man is referred for gigantism. His height is 82 in (208.3 cm) and his weight is 273 lb (123.6 kg), both of which are greater than the 97th percentile. His hands and feet are enlarged, and he has prognathism. A maternal uncle was thought to have had a pituitary adenoma of uncertain type. There is no known family history of calcium disorders or kidney stones. A GH level of 90 ng/mL (90 µg/L) does not suppress adequately during an oral glucose tolerance test.

His serum IGF-1 concentration is 1233 ng/mL (161.5 nmol/L) (reference range, 147-527 ng/mL [19.3-69.0 nmol/L]), his prolactin concentration is 26 ng/mL (1.1 nmol/L), thyroid and adrenal axes are normal, and his serum calcium level is normal. He has a bitemporal visual field defect. MRI of the brain shows a 4.3 × 3.2 × 2.8-cm pituitary adenoma with suprasellar extension.
A germline mutation in which of the following genes is most likely to be responsible for the findings in this patient?

A. **GNAS** (GNAS complex locus) 18%
B. **TBX19** (T-box 19) (previously TPIT) 8%
C. **PROP1** (PROP paired-like homeobox 1) 32%
D. **AIP** (aryl hydrocarbon receptor interacting protein) 25%
E. **MEN1** (menin) 17%

**Question 17**

18. A 35-year-old woman is referred for management of Cushing disease. She has experienced weight gain, depression, and proximal muscle weakness. On physical examination, her blood pressure is 160/98 mm Hg, and she has a centripetal obesity pattern, a rounded face, and purple striae.

Laboratory test results:
- Urinary free cortisol = 325 µg/24 h (897 nmol/d) (reference range, 4-50 µg/24 h [11.0-138.0 nmol/d])
- Serum cortisol (8 AM) = 33 µg/dL (910.4 nmol/L)
- Serum cortisol after 1-mg overnight dexamethasone suppression test = 26 µg/dL (717.3 nmol/L)
- ACTH = 83 pg/mL (18.3 pmol/L) (reference range, 10-60 pg/mL [2.2-13.2 pmol/L])

**Question 18 (1/2)**

MRI shows a 9-mm pituitary adenoma. At surgery, there is partial tumor removal, but considerable intraoperative bleeding leads to premature termination of the operation. Postoperative hormone levels remain elevated, and the patient adamantly refuses further surgery. You elect to begin medical therapy and the patient subsequently develops hypokalemia.

**Question 18 (2/2)**

Which of the following medications is the most likely culprit?

A. Metyrapone 18%
B. Ketoconazole 11%
C. Pasireotide 6%
D. Mitotane 10%
E. Mifepristone 55%

**Question 18**

**Inherited Forms of Pituitary Adenomas**

- **Familial Isolated Pituitary Adenoma (FIPA) syndrome**
  - Autosomal dominant with low or variable penetrance
  - Germline mutations in gene encoding the aryl hydrocarbon receptor-interacting protein (AIP), which functions as a tumor suppressor
  - Such mutations found in ~ 1/3 of FIPA families, most commonly in those with GH & PRL-producing tumors
- **Multiple Endocrine Neoplasia (MEN) Type 1**
  - Mutation in **MEN1** gene
  - Menin a tumor suppressor
  - Occurs with parathyroid and pancreatic tumors
- **Carney Complex**
  - Mutation in type 1A subunit of protein kinase A (PRKAR1A)
  - Pituitary adenoma in 10% (GH), spotty skin pigmentation, myxomas, schwannomas, pigmented nodular adenocortical disease causing Cushing syndrome in 30%

**References**


**Adverse Effects of Mifepristone: Hypokalemia**

- Likely due to mineralocorticoid receptor activation in setting of rising cortisol with glucocorticoid receptor blockade
- Overwhelms the ability of 11β-hydroxysteroid dehydrogenase to convert cortisol to cortisone in the kidney, allowing the high levels of cortisol to activate the mineralocorticoid receptor and causing hypokalemia in some patients
- Hypokalemia is common, but generally mild to moderate and associated with alkalosis and edema

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**Laboratory test results:**

- Testosterone = 218 ng/dL (7.6 nmol/L)
- LH = 2.3 mIU/mL (2.3 IU/L)
- FSH = 1.4 mIU/mL (1.4 IU/L)
- Cortisol (8 AM) = 15.7 µg/dL (433.1 nmol/L)
- Prolactin = 5.7 ng/mL (0.2 nmol/L)
- Free T₄ = 1.2 ng/dL (15.4 pmol/L) (reference range, 0.8-1.8 ng/dL [10.3-23.2 pmol/L])

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**Which of the following is the most appropriate management for this patient?**

A. Visual field testing  
B. Referral to an experienced pituitary surgeon  
C. Another MRI in 1 year  
D. Gamma-knife radiotherapy  
E. Conventional radiotherapy

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**Flow Diagram for Pituitary Incidentalomas**

**Evaluation of Pituitary Function**

- Hyperfunctioning
  - Prolactinoma
  - Other
- Clinically Nonfunctioning
  - <1 cm
  - >1 cm
- R/O Pituitary Hypofunction
- Visual Fields
- Repeat MRI at 1, 2, 5 yrs
- Tumor Growth
- Abnormal Fields
- No Further Studies (?)  
- Surgery

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**Natural History of Untreated Pituitary Incidentalomas**

<table>
<thead>
<tr>
<th></th>
<th>Microadenomas</th>
<th>Macroadenomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>166</td>
<td>356</td>
</tr>
<tr>
<td>Enlarged</td>
<td>17 (10%)</td>
<td>86* (24%)</td>
</tr>
<tr>
<td>Decreased</td>
<td>11 (7%)</td>
<td>45 (13%)</td>
</tr>
<tr>
<td>No Change</td>
<td>138 (83%)</td>
<td>222 (63%)</td>
</tr>
<tr>
<td>Years followed</td>
<td>0.6 - 15.0</td>
<td>0.6 - 12</td>
</tr>
</tbody>
</table>

*Some had tumor enlargement secondary to hemorrhage into the tumor

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**Question 19 (1/2)**

19. An 81-year-old man is referred because a head CT performed after he fell and struck his head showed a pituitary mass. On MRI, this appears to be a 1.2-cm pituitary adenoma with minimal left parasellar extension. He has been feeling well, but in general he thinks he has been slowing down. He has no headaches or vision symptoms. He had a myocardial infarction 10 years ago and currently takes a statin, lisinopril for hypertension, and a baby aspirin. On physical examination, blood pressure is 136/70 mm Hg and pulse rate is 74 beats/min. His skin has normal texture, and his reflexes are normal.

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**Question 19 (2/2)**

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**Question 19**

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20. A 30-year-old woman develops progressive, severe headaches; nausea; vomiting; and fatigue during her 33rd week of pregnancy. She has no notable medical history and was able to become pregnant within 2 months of trying. Her pregnancy course had been smooth until now. Physical examination findings are normal for 33 weeks’ gestation. Her obstetrician persuades the radiologist to perform a noncontrast MRI of her head, and the patient is found to have a diffusely enlarged pituitary, measuring 16 mm in height, without abutment of the optic chiasm.

Laboratory test results:
- Total T₄ = 13 μg/dL (167.3 nmol/L) (reference range, 5.5-12.5 μg/dL [70.8-160.9 nmol/L])
- TSH = 1.3 mIU/L
- Cortisol (8 AM) = 9.0 μg/dL (248.3 nmol/L)
- Prolactin = 137 ng/mL (6.0 nmol/L)

Which of the following is indicated?
A. Start bromocriptine 11%
B. Start cabergoline 10%
C. Refer for transsphenoidal decompression 8%
D. Start hydrocortisone 59%
E. Arrange for an urgent cesarean delivery 12%

21. A 52-year-old woman has had hypopituitarism for 10 years after resection of a nonfunctioning pituitary adenoma. She has been treated with levothyroxine, hydrocortisone, a low-dosage oral contraceptive pill, and daily GH injections. Because her sister recently developed breast cancer, the patient has decided to stop her oral contraceptive.

Lymphocytic Hypophysitis: Clinical Presentation

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass effects</td>
<td>60%</td>
</tr>
<tr>
<td>Headache</td>
<td>60%</td>
</tr>
<tr>
<td>Vision disturbance</td>
<td>40%</td>
</tr>
<tr>
<td>Bitemporal hemianopsia</td>
<td>32%</td>
</tr>
<tr>
<td>Impaired visual acuity</td>
<td>16%</td>
</tr>
<tr>
<td>Diplopia</td>
<td>4%</td>
</tr>
<tr>
<td>Endocrine Dysfunction</td>
<td>80%</td>
</tr>
<tr>
<td>ACTH/adrenal deficiency</td>
<td>65%</td>
</tr>
<tr>
<td>TSH/thyroid deficiency</td>
<td>60%</td>
</tr>
<tr>
<td>GH deficiency</td>
<td>54%</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>40%</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>30%</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>15%</td>
</tr>
</tbody>
</table>

Regarding dosing of her other hormone replacements, which of the following can be expected to occur as a result of stopping the oral contraceptive?

A. Increased levothyroxine dosage 25%
B. Decreased GH dosage 39%
C. Increased GH dosage 10%
D. Increased hydrocortisone dosage 6%
E. Decreased hydrocortisone dosage 20%

**Question 21**

22. A 19-year-old man is asking for a second opinion regarding his current GH treatment. At age 8 years, isolated idiopathic GH deficiency was diagnosed, and he relates that he experienced a substantial increase in height after he started GH treatment. He stopped growing several years ago and he wonders whether he should still be taking GH.

**Question 22 (1/1)**

**How should you advise him?**

A. Stop the GH; he does not need it if he has stopped growing 6%
B. Stop the GH for 1 year and perform a GH stimulation test 11%
C. Stop the GH for 1 month and perform a GH stimulation test 46%
D. Continue the GH at the same dosage for its continued benefits on body composition 3%
E. Decrease the GH dosage to a more typical adult dosage for its continued benefits on body composition 35%

**Question 22**
A 72-year-old man reports fatigue, weight gain, decreased libido, and some difficulty maintaining an erection. He has been well all his life until these symptoms started. He attributes his symptoms to aging, but his wife has urged him to be evaluated. Although he recently retired, he has not changed his lifelong pattern of little exercise. On physical examination, no abnormalities are noted except that he is overweight. The thyroid is not enlarged, and there are no cushingoid features. The patient is well virilized. His blood pressure is 140/92 mm Hg, pulse rate is 60 beats/min, and BMI is 28.2 kg/m².

Laboratory test results:
- Complete blood cell count, normal
- Blood chemistries, normal
- TSH = 0.5 mIU/L
- Free T₄ = 0.5 ng/dL (6.4 pmol/L) (reference range, 0.8-1.8 ng/dL [10.3-23.2 pmol/L])
- Cortisol (8 AM) = 10 μg/dL (275.9 nmol/L)
- Total testosterone (8 AM) = 221 ng/dL (7.7 nmol/L)
- LH = 2.1 mIU/mL (2.1 IU/L)
- FSH = 1.7 mIU/mL (1.7 IU/L)

Which of the following tests is the most important next step?
A. Urinary free cortisol measurement 0%
B. Pituitary-directed MRI 71%
C. Serum free testosterone measurement 13%
D. Ferritin measurement 6%
E. α-Subunit measurement 10%

A 48-year-old man with a history of hypopituitarism after surgical removal of a nonfunctioning pituitary tumor is interested in fertility. He had had normal growth and development and fathered 2 children who are now 12 and 14 years. The 1.3-cm pituitary tumor was found incidentally at age 39 years when a head CT was performed after a motorcycle crash. He currently takes hormone replacement with levothyroxine, hydrocortisone, GH, and transdermal testosterone. He states he has normal libido and erectile function. On physical examination, he is well virilized with testes that are about 20 mL in volume with normal consistency.

Which of the following should be the next step in this patient’s management?
A. Switch from testosterone to hCG injections, 3 times weekly 25%
B. Switch from testosterone to hCG injections, 3 times weekly, and FSH injections, twice weekly 8%
C. Refer for microdissection testicular sperm extraction 3%
D. Obtain a semen analysis 63%
E. Suggest he consider adoption 1%
Are Hypopituitary Men Treated With Testosterone Infertile?

- Hypothesize that exogenous testosterone supplementation in patients was able to maintain levels of intratesticular testosterone sufficient for spermatogenesis in testes previously exposed to normal levels of LH & FSH and with persistent minimal levels of LH & FSH

- Important clinical points:
  - Hypopituitary men treated with testosterone may be fertile
  - Perform semen analysis before embarking on measures to increase spermatogenesis


Are Hypopituitary Men Treated With Testosterone Infertile?

- Identified 3 men with panhypopituitarism treated with testosterone who had sperm counts >20 million and who were fertile
- 12 cases of acquired hypogonadotropic hypogonadism were evaluated
  - 7 had sperm concentrations of >15 million/mL, 2 had sperm concentrations of 1 million/mL, and 3 were azoospermic
  - The 9 cases with evidence of spermatogenesis did not appear to differ from the 6 who were azoospermic either clinically or by need for hormone replacement.
  - Compared with those who were azoospermic, patients with evident spermatogenesis had modestly higher LH levels (3.0 ± 1.0 vs 1.4 ± 1.8 IU/L; and FSH levels (2.7 ± 1.5 vs 1.7 ± 1.7 IU/L)


25. A 73-year-old woman with severe congestive heart failure is admitted to the hospital with altered mental status. On examination, she is disoriented to time and is mildly confused. She has pulmonary edema and 4+ peripheral edema.

Laboratory test results:
- Liver function, normal
- Serum sodium = 121 mEq/L (121 mmol/L)
- Urinary sodium = 14 mEq/L
- Urine osmolality = 373 mOsm/kg (373 mmol/kg)

Question 25 (1/1)

Which of the following treatments is appropriate?

A. Restrict free water intake to less than 1500 mL/24 h 21%
B. Administer 3% saline at a rate of 0.1 mL/kg per h 16%
C. Start demeclocycline 2%
D. Start conivaptan 38%
E. Start a furosemide intravenous drip 23%

Question 25

Conivaptan Pivotal Phase 3 Trial: Serum [Na+] Over 4 Days of Continuous IV Infusion

Placebo (n=29)  IV Conivaptan 40 (n=29)  IV Conivaptan 80 (n=26)

Mean ± SE Serum [Na+] mEq/L

Time (days)

Which of the following treatments is appropriate?

26. A 29-year-old man is referred because a head CT performed in the emergency department after an automobile crash showed an empty sella. A subsequent MRI shows an enlarged sella, minimal tissue along the floor of the sella, with the hypothalamic-pituitary stalk reaching the floor of the sella. He was generally well before the accident. However, he states that he received GH injections for many years as a child and stopped when he completed growth at age 18 years. He has also taken thyroid hormone since age 12 years.

Question 26 (1/1)
Which of the following is the most likely cause of his empty sella?

<table>
<thead>
<tr>
<th>Option</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Trauma-induced pituitary infarction</td>
<td>13%</td>
</tr>
<tr>
<td>B. PROP1 mutation</td>
<td>69%</td>
</tr>
<tr>
<td>C. Burnt-out hypothalamic/pituitary sarcoidosis</td>
<td>3%</td>
</tr>
<tr>
<td>D. Langerhans cell histiocytosis</td>
<td>13%</td>
</tr>
<tr>
<td>E. Hemochromatosis</td>
<td>2%</td>
</tr>
</tbody>
</table>

Question 26

27. You are called to see a 20-year-old man in the rehabilitation hospital 3 months after a motorcycle crash. He suffered extensive head injuries, including a basal skull fracture, and has been recovering from brain/cranial surgery. He seems to be regaining his strength more slowly than expected. However, he is eating and drinking from a tray without assistance. Over the past week, his serum sodium concentration has gradually fallen to 129 mEq/L (129 mmol/L). His serum urea nitrogen concentration is 6 mg/dL (2.1 mmol/L), and his creatinine concentration is 0.5 mg/dL (44.2 μmol/L).

Which of the following is the most likely cause of his hyponatremia?

<table>
<thead>
<tr>
<th>Option</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Hypopituitarism</td>
<td>21%</td>
</tr>
<tr>
<td>B. Syndrome of inappropriate antidiuretic hormone secretion</td>
<td>47%</td>
</tr>
<tr>
<td>C. Excessive diuretic use to prevent brain swelling</td>
<td>3%</td>
</tr>
<tr>
<td>D. Cerebral salt wasting</td>
<td>20%</td>
</tr>
<tr>
<td>E. Iatrogenic water intoxication</td>
<td>10%</td>
</tr>
</tbody>
</table>

Question 27

28. A 64-year-old man is found to have a 2.3-cm sellar mass abutting the optic chiasm after his ophthalmologist identified a left eye visual field defect. MRI shows a relatively normal-sized sella with a large mass extending in a suprasellar fashion. In retrospect, he has had poor energy, frequent urination, increased thirst, and a 46-lb (20.9-kg) weight gain over the past 2 years. Testing reveals a prolactin concentration of 42.7 ng/mL (1.9 nmol/L) (similar on dilution), panhypopituitarism, and diabetes insipidus.

Question 28
Which of the following is the most likely diagnosis?

A. Gonadotroph adenoma  18%  
B. Prolactinoma  2%  
C. Craniopharyngioma  37%  
D. Silent corticotroph adenoma  14%  
E. Langerhans cell histiocytosis  29%

Question 28

29. An internist refers to you a 26-year-old man for suspected diabetes insipidus. He reports a constant sense of thirst, and he believes he drinks more fluids and urinates more often than other people.

Laboratory test results:
- Plasma glucose (fasting) = 89 mg/dL (4.94 mmol/L)
- 24-hour urine total volume = 3.5 L
- Urine osmolality = 70 mOsm/kg (70 mmol/kg)

A fluid deprivation test over 4 hours results in a 2.9-lb (1.3-kg) decrease in body weight, a rise in serum sodium from 140 to 145 mEq/L (140 to 145 mmol/L), and a rise in serum osmolality from 283 to 295 mOsm/kg (283 to 295 mmol/kg). The osmolality of urine collections over this period increases from 70 to 525 mOsm/kg (70 to 525 mmol/kg). At the end of the 4-hour period, a subcutaneous injection of DDAVP (2 mcg) is administered, and 1 and 2 hours after the injection, his urine osmolality rises to 553 and 576 mOsm/kg (553 and 576 mmol/kg), respectively.

On the basis of these results, which of the following would be the most effective therapy for this patient?

A. Amiloride  7%  
B. Thiazide diuretic  9%  
C. Indomethacin  1%  
D. Referral for psychiatric evaluation  64%  
E. DDAVP (desmopressin)  19%

Question 29

Urinary Responses to Fluid Deprivation and Exogenous AVP

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Max U_{\text{osm}} w/ dehydration</th>
<th>U_{\text{osm}} after AVP % change in U_{\text{osm}}</th>
<th>U_{\text{osm}} ↑ after AVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1068 ± 69</td>
<td>979 ± 79 -9 ± 3</td>
<td>&lt;9%</td>
</tr>
<tr>
<td>Complete DI</td>
<td>168 ± 13</td>
<td>445 ± 52 183 ± 41</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Partial DI</td>
<td>438 ± 34</td>
<td>549 ± 28 23 ± 5</td>
<td>&gt;9% &lt;50%</td>
</tr>
<tr>
<td>Nephrogenic DI</td>
<td>124</td>
<td>174 42</td>
<td>&lt;50%</td>
</tr>
<tr>
<td>Comp. water drinking</td>
<td>738 ± 53</td>
<td>780 ± 73 5 ± 2</td>
<td>&lt;9%</td>
</tr>
</tbody>
</table>


Question 29 (2/2)