Metabolism and Reproduction Case Based Learning 1: Facilitator Version

Last Revised: July, 2020

**Objectives**

Additional objectives and pertinent USMLE topics to be released after the session.

* Outline treatment for active Tb and latent Tb in patients not infected with HIV.
* Elicit an appropriate OB/GYN history.
* List a differential diagnosis for oligomenorrhea/secondary amenorrhea and describe how to diagnose this problem

Additional objectives: To be posted after the CBL session

1. Draw the hypothalamic-pituitary-gonadal axis and describe how prolactin, GnRH, FSH/LH and estradiol each provide feedback within the axis.
2. Indicate how the anterior pituitary and posterior pituitary differ in regards to how secretion of hormones is regulated.
3. Describe the primary pharmacologic treatment for hyperprolactinemia and explain how these drugs limit prolactin release.
4. Diagram a simple JAK-STAT signaling pathway.

**Overview:** Case 1 is a patient originally diagnosed with tuberculosis in a previous course. The point of this case is that physicians often need to see patients to follow up on their progress and, in this case, to adjust medications as per protocol. In Case 2, the patient has a prolactin-secreting adenoma of the pituitary gland. Encourage students to develop a broad differential diagnosis and narrow it based on her history, symptoms, labs, and imaging studies. They should cover basic biology of the hypothalamus-pituitary axis, including feedback loops and basic cell biology. Underlying both cases are social aspects that students should consider as they go through each case. This is a married couple who has one son (age 14) in school. They communicate with each other in Spanish, while the wife speaks and reads conversational English. She reads Spanish at a 11th grade level, and the husband reads Spanish at a 5th grade level. The family has a combined income in the range of $20,000 to $24,999. The nurse and MA are bilingual in Spanish and English and have arranged for a trained medical interpreter. (Note: “translation” is for written language; “interpretation” is for oral language. This may be an opportunity to discuss the Culturally and Linguistically Appropriate Services (CLAS) Standards <https://health.utah.gov/disparities/class-standards.html> )

## Resources

##### Many resources are available electronically through the Eccles Library eBook collections:

<http://campusguides.lib.utah.edu/ebooksHealthSciences>

## Case 1

*All items in blue are only on the facilitator guide*

Today, husband and wife, Alberto (H&D case 5) and Carmen, are here. They have come for appointments on the same day because Alberto is more comfortable with his wife there since he has limited English proficiency and she speaks and reads conversational English. The family immigrated to the U.S. 2 years ago from Chihuahua, Mexico with their daughter, who was age 6 at the time. He began working on a farm and she works part-time as an Aide at a Head Start program. They live in a mobile home with his family in Louisville, Kentucky. On the farm Alberto’s job consists mainly of planting and harvesting corn and soybeans. He does not smoke, drink alcohol, or use any drugs recreationally. No one else in his household has been sick.

Alberto comes for a two-month follow-up after initiation of RIPE therapy (a four drug regimen) for active tuberculosis sensitive to all RIPE drugs. He indicates that he continues taking all of his anti-Tb drugs and hasn’t missed a dose. He states that he is feeling much better and hasn’t had cough or hemoptysis since his previous visit one month ago. Labs two weeks ago demonstrated normalization of his liver enzymes. The MA is bilingual in Spanish and English and has arranged for a trained medical interpreter. When you enter the room, the nurse is speaking directly to the interpreter in English and talks about the couple in third person.

### Medications:

1. Isoniazid 300 mg once daily
2. Rifampin 600 mg once daily
3. Pyrazinamide 1500 mg once daily
4. Ethambutol 1200 mg once daily
5. Pyridoxine 25 mg once daily

### Physical Exam:

**VITAL SIGNS:** T 37.3, HR 78, RR 18, BP 108/58, SaO2 95% on room air, Wt 64 kg (increased 4 kg since Tb diagnosis), Ht. 70 in.

**HEENT** (head/eyes/ears/nose/throat)**:**  Pupils are equal and reactive with normal conjunctivae. Ears and nose normal. Poor dentition. Oropharynx is clear of erythema and lesions.

**NECK:** Supple. Jugular venous pulsation is estimated to be 1 cm above the sternal angle (normal right heart pressure). There is no lymphadenopathy.

**CHEST/LUNGS:** Occasional crackles in the right middle and upper posterior fields (expected residual inflammation from resolving Tb infection). Otherwise, clear to auscultation. No dullness to percussion.

**HEART:** Normal rhythm and no murmur. No pericardial rub. Normal S1, S2; no gallop. (all normal)

**ABDOMEN:** Soft, non-tender, non-distended. No liver or spleen enlargement. Normal bowel sounds. No CVA tenderness (CVA: costovertebral angle; area of back overlying kidneys).

**EXT:** Pulses 2+ bilaterally. Capillary refill < 3 seconds. No lower extremity edema. (all normal)

**NEURO:** Cranial nerves individually assessed and are functioning normally. Motor strength 5/5 in upper and lower extremities. Sensation and proprioception intact. Deep tendon reflexes 2+ bilaterally symmetric at the patellar tendons. (all normal)

**SKIN:** No lesions, abnormal moles, or discoloration noted.

### Discuss the case

**1. Summarize the important aspects of the case.**

* Alberto was previously diagnosed with active tuberculosis (Tb) about two months ago. He is clinically improving based on his symptoms and weight gain. And he continues to take his medications. Students who compared this physical exam to the previous exam (H&D case 5) will note that his heart rate and respiratory rate are now normal and there is no longer evidence of muscle wasting.
* Discuss the appropriate ways to communicate with patients who have limited English proficiency and through a trained medical interpreter, including the roles of conduit of communication, clarifier, and cultural broker for an interpreter. How would the students approach the nurse about using a more patient-centered approach to communicating through the interpreter, while maintaining a good working relationship? Reference:
  + <https://www.health.utah.gov/disparities/clas-mental-health/interpreters/index.htm>

**2. What studies do you want at this two-month follow-up appointment?**

* Those who came prepared will note that therapy for active Tb includes intensive and continuation phases.
  + The intensive phase usually consists of four drugs (rifampin, isoniazid, pyrazinamide, and ethambutol = RIPE) administered for two months. At the end of the intensive phase (today), a repeat clinical assessment should be performed along with repeat chest radiograph and repeat sputum for acid-fast bacilli (AFB) smear and culture.
  + The continuation phase (regimen beyond the first two months) usually consists of two drugs (isoniazid and rifampin) administered for at least four additional months, for a total of six months.
* At this two-month visit, standard recommendations suggest that they should order a CXR and collect sputum for AFB stain and culture. Once they indicate this, give them the following password.

M&R CBL 1 Case 1 Reveal 1

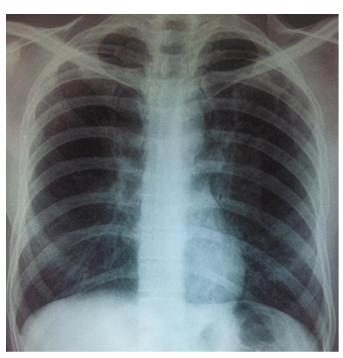
## Password: 8421

## Reveal 1

**Sputum AFB stain:** Adequate sample. Negative for AFB.

**Sputum AFB culture:** Results can take up to six weeks.

**Current CXR**



**CXR at diagnosis two months ago**



**3. Interpret the data.**

* There is no evidence of Tb in his sputum by AFB stain.
* Although there are differences in technique (which is always the case) his CXR has significantly improved compared to the prior CXR. Students should point out the cavitary lesion (red arrow) and surrounding infiltrate in the right hilum and the infiltrate in the right upper lobe (green arrow) in his diagnosis CXR. Student version doesn’t have arrows.

**4. What do you want to do next?**

* He has clinically improved, his CXR has improved, and there is no evidence of Tb in his sputum by AFB stain. The next step is to convert him to continuation (or maintenance) therapy by stopping the pyrazinamide and ethambutol. Isoniazid and Rifampin should be continued as should the pyridoxine.

**5. Why is he taking pyridoxine?**

* Isoniazid interferes competitively with pyridoxine (vitamin B6) metabolism by inhibiting the formation of the active form of the vitamin.
  + VitB6 is a cofactor in a number of biological processes, including neurotransmitter synthesis. As such, INH can lead to peripheral neuropathies in susceptible individuals (about 2% of patients taking INH) and is usually given to most patients to avoid this consequence.
  + They also learned in an earlier course that vitB6 is also a cofactor in heme synthesis. So without pyridoxine, INH can lead to microcytic anemias.

## Case 2

Chief Complaint: “My periods aren’t normal and I’m really tired.”

### HPI:

Carmen is a 34-year old woman who attempts to describe a sensitive chief complaint in conversational English. When she communicates through an interpreter, she clarifies that she has had she has had irregular periods for almost one year. At first the periods were just “lighter” than normal but continued to occur at regular intervals. For the last 6 months there has been longer duration between her periods and she can no longer predict when they will begin. It has been almost 2 months since she has had any menstrual bleeding. She tells you that she has taken three home pregnancy tests because she keeps thinking she might be pregnant and they have all been negative. She has occasional cramps before a period begins but this is normal for her and there is no other associated pain.

In addition to the change in her menses, Carmen tells you that she is increasingly fatigued, has diminished libido and has occasional headaches. A coworker did an online search of her symptoms and found that she might have thyroid disease, which Carmen is concerned about.

### PMH:

No ongoing or chronic medical problems for which she sees a doctor.

Mild seasonal allergies and occasional sinus infections, usually in the spring.

No hospitalizations except for childbirth.

No significant childhood illnesses

### PSH:

None

### Meds:

Isoniazid 300mg once daily (for latent Tb). Started when her husband was diagnosed with Tb and she had a positive tuberculin skin test, but a normal CXR.

Pyridoxine 25mg once daily

Takes multivitamins about once a week

No medical allergies

### FH (family history):

Mother 60 years old in good health

Father 62 years old with obesity, high blood pressure and “early” diabetes

No chronic medical problems in other family members

### SH (social history):

Married for 15 years

Works as a prep cook in a restaurant

One son, age 14 in good health

No smoking

Drinks a beer occasionally

No history of illicit drug use

### ROS (review of systems):

General: 5-pound weight gain in last 6 months “because I’m too tired to exercise.” No sweats or chills, no fever. Increased fatigue overall, no change in appetite

HEENT: No perceived change in vision or hearing, no sore throat

Neck: No perceived fullness or pain

Chest/Lungs: No cough, no difficulty breathing

Heart: No palpitations, no chest pain

Abdomen: No change in bowel habits. No nausea or vomiting

GU (genitourinary): No change in urinary habits. No pain with urination

Extremities: No pain in joints or perceived swelling

Skin: No rash noted

Neuro: Occasional headaches “all over my head” every few days. These improve with ibuprofen. No perceived weakness.

### Physical Exam:

**Temp** 36.8; HR 80; RR 14; BP 110/65; BMI 23 (all normal)

**General:** Awake, pleasant, in no distress

**HEENT:** PERRLA (normal pupil exam), EOMI (normal eye movements), OP (mouth) clear without lesions

**Neck:** Supple, no mass, no thyromegaly

**Lungs:** CTA (normal breath sounds) bilaterally, no difficulty breathing

**Heart:** RRR (regular rate and rhythm), no murmur

**Abd:** Soft, ND (not distended), NT (not tender), no mass

**Ext:** Warm, no edema, full ROM (range of motion)

**Skin:** Normal turgor, no rash

**Neuro:** Normal strength and sensation throughout, 2+ patellar reflexes, normal gait (all normal)

1. **Summarize the important historical findings in this case and indicate other history you would like to know.**

Carmen has had about one year of abnormal periods. For the first six months, she had lighter than normal periods and for the last six months, she has had infrequent periods. Her last period was about two months ago. She has also experienced fatigue, reduced libido, and occasional headaches. They should want to know more about her OB/GYN history. When they come to this conclusion, ask them what specific information they would like. Make sure that they list most of the information in the reveal below before giving them the password.

M&R CBL 1 Case 2 Reveal 1

## Password: 3972

## Reveal 1

**OB/GYN History**

First menses (period) at age 12 (normal)

Periods became regular within about one year and have always been predictable except when she has been pregnant

Typically 30 days between periods and flow for ~5 days (normal)

Used oral contraceptives when she was younger. After the birth of her 2nd child she used Nuva Ring (etonogestrel/ethinyl estradiol vaginal ring) but had side effects from it so discontinued its use. No current birth control.

G2P2 (pregnant twice, two live births after 24wks)

First child was SVD (spontaneous vaginal delivery) at 37 weeks; second child was SVD at 39 weeks. No complications at birth for either child

No history of abnormal Pap smear (last was “a few” years ago)

No history of STI (sexually transmitted infection)

Does not conduct breast self-exam

1. **Is there anything else you would like to know about the Physical Exam?**

**Give answers orally only if asked:**

**GYN exam**

* No external lesions
* No vaginal discharge
* Cervix non-tender to palpation, no masses palpable on bimanual exam
* Pap smear and cultures normal

**Breast exam**

* No masses palpable
* No nipple discharge (FYI: milk discharge can, but does not usually, occur with prolactinoma)

**Visual Fields** (don’t give them this information unless they specifically ask for it)

* Slight decrease in bilateral peripheral visual fields with testing

1. **On the white board, make a problem list for this patient. What is the differential diagnosis?**

Problem list: abnormal menses, fatigue, reduced libido, headaches, peripheral visual field reduction (if they asked about this).

Differential diagnosis: There are a number of causes of each problem. To narrow the possibilities, students should consider how the problems might be related and focus on her primary complaint (abnormal menses).

* Abnormal menses can be divided into three categories (see below). Have the students define the three categories, indicate which one she has, and provide possible causes of each. They should discuss evidence for or against each possible cause (noted) and indicate the most likely causes. The big picture: most causes are due to disruptions/alterations of the hypothalamus 🡪 pituitary 🡪 ovary 🡪 uterine axis.
  + Primary amenorrhea (never had menses): She doesn’t have this. Possible causes:
    - Hypergonadotropic hypogonadism = gonadal development failure; Turner Syndrome
    - Hypogonadotropic hypogonadism = hypothalamic failure secondary to inadequate GnRH synthesis
  + Secondary amenorrhea (had normal menses, but menstruation stops for more than 6 months): She doesn’t quite meet this criterion. Causes are the same as oligomenorrhea.
  + Oligomenorrhea (infrequent periods [from 35 days up to 5 months apart): She has this. The most common possible causes:
    - Pregnancy: this is a possibility, she is not taking birth control, but has had negative home pregnancy tests
    - Hypothalamic dysfunction. Possible causes:
      * GnRH deficiency (uncommon)
      * Tumors (craniopharyngioma): her headaches are consistent with this
      * Inflammatory or infiltrative diseases of the hypothalamus
      * Weight loss, exercise, nutritional deficiency: no evidence of this
    - Pituitary Disease
      * Hyperprolactinemia/prolactinoma: consistent with all of her symptoms
    - Ovarian Disease
      * Premature ovarian failure (menopause)
      * Tumors: no evidence by physical exam (PE), but PE is not very sensitive
      * Polycystic ovary syndrome (PCOS): no evidence by (not very sensitive) PE
    - Other: Thryoid disease, uncontrolled diabetes: Thyroid disease is a possibility
* Their focus should be on oligomenorrhea and its causes. They might jump right to prolactinoma, but encourage them to think broadly. For her, the most likely possibilities are pregnancy, hypothalamic disease (tumor or infiltrative disease), pituitary disease/prolactimoma, ovarian disease, and thyroid disease.

1. **How would you go about determining the cause of her oligomenorrhea?**

For each test suggested, have them explain why the result would lead to oligomenorrhea. If they are unsure of how to proceed, they can look up standard evaluation recommendations that focus on three of the main categories above: A pregnancy test to rule out pregnancy, FSH combined with estrogen to test the pituitary-ovarian axis, TSH to evaluate thyroid function, and a prolactin level to test for hyperprolactinemia. Once they have identified these tests, give them the following reveal.

M&R CBL 1 Case 2 Reveal 2

## Password: 8392

## Reveal 2

|  |  |  |
| --- | --- | --- |
| **TEST** | **RESULT** | **RANGE** |
| Urine Pregnancy Test | Negative |  |
| FSH | 3 U/L | 4-30 U/L |
| Prolactin | 135 ng/ml | <20 ng/ml |
| Estradiol (E2) | 80 pg/ml | 94-436 pg/ml |
| TSH | 2.8 mU/L | 0.5-5.0 mU/L |

Abnormal values not highlighted in student copy

1. **How do you interpret the labs?**

She’s not pregnant. Prolactin is very high. (A measurement this high suggests a prolactin-secreting pituitary adenoma.) FSH and E2 are also low, but TSH is normal. Their focus should be on the high prolactin level, but they should also realize that the reduced FSH/E2 caused her oligomenorrhea and reduced libido)

**Why are the FSH and estradiol levels low?**

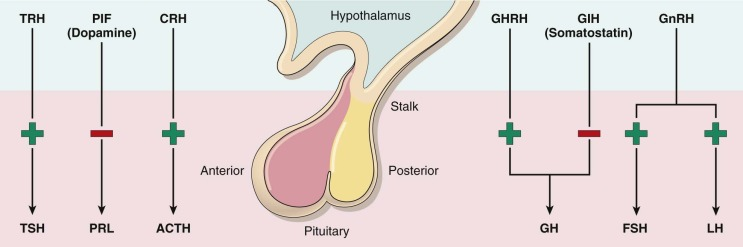
Since the hypothalamus is apparently functioning normally (based on the normal TSH), there are two possibilities.

* First, excess prolactin might reduce FSH secretion and, consequently, E2 production. This is, in fact, what happens. High levels of prolactin decrease GnRH secretion from the hypothalamus leading to a decrease in FSH secretion from the pituitary, which reduces estradiol production by the ovary.
* Second, a tumor mass effect in the pituitary could also directly decrease FSH production. Although this is a possibility, TSH would likely be low too.

1. **On the white board, diagram the hypothalamus-pituitary axis and indicate how the anterior pituitary and posterior pituitary differ in regards to how secretion of hormones is regulated.**

See diagram below (Figure 24-1 from Robbins).

* The posterior pituitary is an extension of the hypothalamus. Two peptide hormones, oxytocin and antidiuretic hormone (ADH, also called vasopressin), are synthesized in the hypothalamus, stored in the posterior pituitary, and then secreted.
* The anterior pituitary constitutes about 80% of the gland. Unlike the posterior pituitary, production of its hormones occurs in the pituitary and is controlled by positively and negatively acting factors from the hypothalamus which are carried to the anterior pituitary by a vascular system.



Robbins Figure 24-1: Hormones released by the anterior pituitary. The anterior pituitary releases five hormones that are in turn under the control of various stimulatory and inhibitory hypothalamic releasing factors. TSH, thyroid-stimulating hormone (thyrotropin); PRL, prolactin; ACTH, adrenocorticotropic hormone (corticotropin); GH, growth hormone (somatotropin); FSH, follicle-stimulating hormone; LH, luteinizing hormone. The stimulatory releasing factors are TRH (thyrotropin-releasing hormone), CRH (corticotropin-releasing hormone), GHRH (growth hormone-releasing hormone), GnRH (gonadotropin-releasing hormone). The inhibitory hypothalamic influences comprise PIF (prolactin inhibitory factor or dopamine) and growth hormone inhibitory factor (GIH or somatostatin).

Students should note each hormone released by the pituitary and the corresponding releasing factors from the hypothalamus. They should also note the function of each factor released by the pituitary and its target organ (if applicable):

Thyroid stimulating hormone (TSH): promotes thyroxin (T4) production by thyroid

Prolactin (PRL): stimulates mammary gland lactation (and has other properties)

Adrenocorticotropic hormone (ACTH): stimulates cortisol production by adrenal glands

Growth hormone (GH): has anabolic (growth) effects throughout the body.

Follicle-stimulating hormone (FSH): regulates development, growth, pubertal maturation, and reproductive processes

Luteinizing hormone (LH): triggers ovulation (women) or testosterone production (men)

Oxytocin: stimulates milk ejection and uterine contraction (and others)

ADH: promotes water reabsorption in the kidneys

1. **After they have discussed the H-P axis, provide them with the following pass code for the following reveal:**

M&R CBL 1 Case 2 Reveal 3

## Password: 5631

## Reveal 3

In a theoretical experiment using mice, serum levels of anterior pituitary hormones were measured and then the hypothalamus stalk was transected to separate it from the pituitary gland. Serum levels of the hormones were measured six hours later. Results are shown below. Explain the data.

|  |  |  |
| --- | --- | --- |
| **HORMONE** | **SERUM LEVEL BEFORE TRANSECTION** | **SERUM LEVEL AFTER TRANSECTION** |
| GH | 2.0 ng/mL | 0.2 ng/mL |
| PRL | 10.7 ng/mL | 67.7 ng/mL |
| ACTH | 16.3 pg/mL | 2.1 pg/mL |
| FSH | 7.8 IU/L | 1.5 IU/L |
| LH | 6.0 IU/L | 1.7 IU/L |

(Unfortunately the data are made up because the experiment was done in the 1970s, making it difficult to locate the original data.) The students should note that all levels drop following transection except PRL, which increases. The others drop because they are positively regulated by the hypothalamus and, without its influence, they have no stimulus for release. In contrast, cells producing PRL (lactotrophs) are unique among endocrine cells in having a high basal secretory activity. This partly explains why regulation of prolactin secretion is also distinct from the other pituitary hormones in that the predominant action of the hypothalamus is to tonically inhibit pituitary PRL release. Make sure that they conclude from the data that PRL-secreting cells exhibit high basal secretory activity and then move on to the next question.

1. **Prolactin inhibits its own secretion by promoting dopamine production. Propose a simple scheme for this regulation and compare it to how FSH production is regulated by estrogen.**

Students should draw on the white board something like the figure below. PRL regulates its secretion by a short feedback loop, while FSH production is regulated by a more common end-product feedback loop through estrogen (E2) produced by the ovary. Ask them to focus on the PRL feedback loop and provide more detail about receptors. They should specifically note that there should be PRL receptors (PRL-R) on cells in the hypothalamus and dopamine (DA) receptors on lactotroph cells in the anterior pituitary. (FYI: The PRL gains access to the hypothalamus through the CSF, which it enters via the choroid plexus, and DA receptors in the anterior pituitary inhibit adenylyl cyclase activity, which reduces PRL transcription.)

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1. **The prolactin receptor signals through the JAK-STAT pathway. Can you hypothesize a general mechanism by which this pathway can affect dopamine?**

They learned about the JAK-STAT pathway in an earlier course (MCC). First have them describe the general functions of JAK and STAT. JAKs are protein tyrosine kinases (JAK=janus kinases) while STATs are transcription factors. They should propose that when PRL binds to its receptor in the hypothalamus, dopamine production increases: PRL 🡪 PRL receptor 🡪 JAK 🡪 STAT 🡪 dopamine synthesis. Ask them how this might occur. They should point out that dopamine is a molecule that is synthesized, so JAK-STAT signaling likely increases expression or activity of enzymes involved in its synthesis. That is as far as they need to go with this, but specifically, the primary target is tyrosine hydroxylase, which catalyzes the rate limiting step in DA synthesis.

Once they have proposed a mechanism give them the next reveal:

M&R CBL 1 Case 2 Reveal 4

## Password: 4393

## Reveal 4

Complete the following table with hypothetical alterations. Focus your answers on changes in DA, PRL, and/or downstream effects in target tissues.

|  |  |  |
| --- | --- | --- |
| **ALTERATION** | **CELL WITH ALTERATION** | **EFFECT OF ALTERATION** |
| *D2R* gene deletion | anterior pituitary lactotroph | incr. DA; incr. PRL; incr. lactation |
| PRL-R gene deletion | hypothalamus | decr. DA; incr. PRL; incr. lactation |
| activating JAK mutation | hypothalamus | incr. DA; decr. PRL |
| activating JAK mutation | mammary gland | incr. lactation |
| activating JAK mutation | bone marrow erythroblast | polycythemia vera |

DA = dopamine; PRL = prolactin; D2R = dopamine receptor; PRL-R = prolactin receptor; lactotroph = cells in the anterior pituitary that secrete PRL.

1. **How do you want to proceed regarding the high prolactin level?**

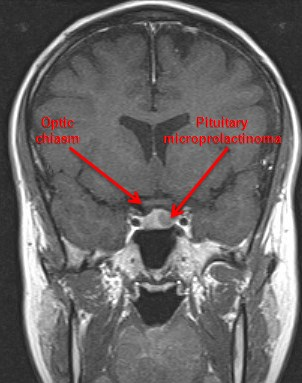
With the possibility of a prolactin-secreting tumor, they should reason that brain imaging is necessary to evaluate the pituitary gland. An MRI is the best imaging choice. (FYI: Some advocate a second measurement of prolactin before proceeding because stress can also increase prolactin levels.)

M&R CBL 1 Case 2 Reveal 5

## Password: 6362

## Reveal 5

The patient undergoes an MRI of the brain and is found to have a 0.7cm mass in the pituitary gland.



The MRI shows that she has a (prolactin-secreting) pituitary tumor.

1. **Propose two ways to treat this patient’s prolactinoma?**

* A dopamine agonist drug should usually be the first treatment for patients with hyperprolactinemia of any cause, including prolactinomas (lactotroph adenomas) of all sizes, because these drugs decrease serum prolactin concentrations, and >90% of the time, decrease the size of prolactinomas.
  + - Cabergoline and bromocriptine are the main pharmacologic agents used.
* If the tumor fails to respond to dopamine agonists or the patient doesn’t tolerate the meds, the tumor can be resected. If there is a significant amount of residual tumor, radiation treatment is usually administered. (Note that she is probably uninsured, so only certain hospitals would offer surgery.)

**12. How long should she take the INH?**

To treat latent tuberculosis, she should take the INH for a total of nine months.

**13. Is there a routine drug toxicity monitoring for INH that you might consider for this patient?**

INH can cause liver toxicity and there is no indication that she has had her liver function tested since starting INH two months ago. So they should order a liver function panel. Once they have indicated this, give them the following password.

M&R CBL 1 Case 2 Reveal 6

## Password: 3218

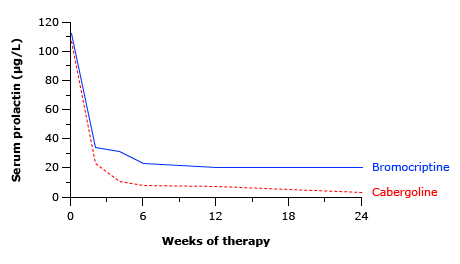
## Reveal 6

All liver function labs are normal. No change in INH is necessary.

|  |  |  |
| --- | --- | --- |
| Liver Function Tests | Value | Normal Range |
| AST | 58 units/L | 17 – 59 units/L |
| ALT | 70 units/L | 21 – 72 units/L |
| Alkaline Phosphatase | 104 units/L | 38 – 126 units/L |
| Total Protein | 7.6 g/dL | 6.3 – 8.2 g/dL |
| Albumin | 3.8 g/dL | 3.5 – 5.0 g/dL |
| Total Bilirubin | 1.1 mg/dL | 0.2 – 1.3 mg/dL |
| Direct Bilirubin | 0.2 mg/dL | 0.0 – 0.2 mg/dL |

After discussions with Carmen and her husband, you prescribe cabergoline 0.25mg twice a week, a dose typically used to treat her condition. You indicate that the principal side effects of dopamine agonist drugs are nausea, postural hypotension, and mental fogginess. Less common side effects include nasal stuffiness, depression, Raynaud phenomenon, alcohol intolerance, and constipation.  She returns to clinic in one month for a follow up appointment and brings the following labs drawn a few days before her appointment. Below the labs are results from a study comparing patient response to bromocriptine and cabergoline (from UpToDate). While waiting for the interpreter, you review the labs:

|  |  |  |  |
| --- | --- | --- | --- |
| **Test** | **Prior Result** | **New Result** | **Range** |
| **Urine Pregnancy Test** | Negative | Negative |  |
| **Prolactin** | 135 ng/ml | 92 ng/ml | <20 ng/ml |



**14. Interpret the labs.**

* The prolactin is reduced, but not as much as would be expected from the clinical study.

**15. Can you think of reasons why she hasn’t responded as well as expected?**

* The main possibilities are resistance to the medication or not taking it as prescribed. Clarify specifics of non-adherence, underlying causes of this behavior, and patient-centered approaches to improving these behaviors.
  + Resistance to the medications: There are a number of possibilities that students should consider, including altered GI absorption, altered/enhanced drug metabolism, and several alterations in lactotroph cells (e.g. dopamine receptor (DA-R) downregulation, changes in DA-R downstream signaling, altered prolactin transcription, etc.). Students shouldn’t spend much time here.
  + Non-adherence: Students should spend more time here. About 25% of new prescriptions are never filled and patients who fill a prescription often take it less often than prescribed or don’t finish the prescription. Many of these patients make a rational decision not to take their medicine based on their knowledge, experience and beliefs. The eight most common reasons for intentional non-adherence are listed below. Students should list them on the board and discuss how cultural and socioeconomic issues might have potentially resulted in Carmen being non-adherent. Students should also critically consider the potential for stigmatizing a patient because of a nondescript label such as “non-adherent” or “non-compliant.”
    - **Fear.** Patients may be frightened of potential side effects (e.g mental fogginess).
    - **Cost.** Patients may not fill medications in the first place or ration what they do fill to extend their supply. (Costco wholesale cost for cabergoline or bromocriptine is ~$50/month)
    - **Misunderstanding.** Patients may not understand the need for the medicine, the nature of the side effects or the time it will take to see results. (Note that the interpreter’s skill as a cultural broker is very important in this process.) This is particularly true for patients with chronic illness, because taking a medication every day to reduce the risk of something bad happening can be confusing. Failure to see immediate improvement may lead to premature discontinuation.
    - **Too many medications.** The greater the number of different medicines prescribed and the higher the dosing frequency, the more likely a patient is to be non-adherent.
    - **Lack of symptoms.** Patients who don’t feel any differently when they start or stop their medicine might see no reason to take it.
    - **Worry.** Concerns about becoming dependent on a medicine also lead to non-adherence.
    - **Depression.** Patients who are depressed are less likely to take their medications as prescribed.
    - **Mistrust.** Patients may be suspicious of their doctor’s motives for prescribing certain medications because of past negative experiences with healthcare providers, recent news coverage of marketing efforts by pharmaceutical companies influencing physician prescribing patterns.

Once they have covered these topics, move on to the final reveal.

M&R CBL 1 Reveal: Case follow-up, Objectives, and Pertinent USMLE outline Topics

## Password: 587

**Case follow-up:** Through an interpreter, Carmen indicates that she was not experiencing side effects from the cabergoline. However, she was barely able to afford her initial cabergoline prescription so she was taking it only once per week to prolong her supply. Please take a few moments to discuss options to help reduce her out-of-pocket cost. (FYI: cabergoline is generic.)

* Use a cheaper med: the other possible (generic) medication, bromocriptine, is similarly expensive.
* A search for cabergoline patient assistance programs somehow leads to Pfizer, which does not have an assistance program for cabergoline (and sells a more expensive, brand name version). Further down the search result list are other possible options such as [www.needymeds.org](http://www.needymeds.org) that might help depending on her income and insurance status (e.g., critical/illness insurance which may not cover all of her healthcare needs). It may be an issue if she is uninsured, since some of these programs (e.g. needymeds.org) surprisingly can require that a patient carry some form of insurance. Legal US residency, however, is not necessarily a requirement.

**Additional objectives:**

1. Draw the hypothalamic-pituitary-gonadal axis and describe how prolactin, GnRH, FSH/LH and estradiol each provide feedback within the axis.
2. Indicate how the anterior pituitary and posterior pituitary differ in regards to how secretion of hormones is regulated.
3. Describe the primary pharmacologic treatment for hyperprolactinemia and explain how these drugs limit prolactin release.
4. Diagram a simple JAK-STAT signaling pathway.

### Pertinent USMLE Topics:

### Female Reproductive System & Breast

Menstrual and endocrine disorders

Abnormal uterine bleeding, including perimenopausal; absence of menstruation (primary amenorrhea, secondary amenorrhea including undiagnosed pregnancy)

### Endocrine System

##### Organ structure and function

Hypothalamus, posterior and anterior pituitary gland

Pituitary disorders:

Neoplasm, benign and malignant (pituitary adenomas, craniopharyngioma, metastatic disease); prolactinoma and hyperprolactinemia, including infertility due to these disorders

##### Hypothalamic endocrine disorders

**Social Sciences**

Communication and interpersonal skills, including health literacy and numeracy, cultural Competence

Use of an interpreter

Health care policy

Health care disparities: race/ethnicity; socioeconomic status

Access to care: critical access systems or hospitals