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An Unexpected Cause of Amenorrhea

Urgent message: The simplest explanation for a mundane symptom may not always reflect the correct diagnosis. Urgent care providers should consider all the possibilities in order to reach the correct conclusion as early as possible, or risk missing a more serious underlying diagnosis.

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Introduction

Sometimes a simple complaint results in a common diagnosis, but other times a rare diagnosis will be discovered. The following case illustrates the importance of considering a wide differential and obtaining appropriate follow-up. Further morbidity was prevented by the vigilance and care of the urgent care provider.

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Case Presentation: Two Months Earlier

A 28-year-old female presents with complaints of a missed period with last menstruation 6 weeks ago. Her menstrual cycle is normally regular. She has no other complaints. She is a student and lives by herself. She denies smoking, using illicit drugs, or drinking alcohol. She had a healthy childhood and has never been hospitalized. No past surgical history. Denies being sexually active. Patient denies possibility of being pregnant. She denies family history of hypothyroidism. She has never been on any prescription drugs and is not allergic to anything. Review of systems is positive for nausea and intermittent left breast tenderness; otherwise, negative for fatigue, fever, chills, weight loss, headache, vision changes, upper respiratory symptoms, chest pain, shortness of breath, abdominal pain, bowel movements or urinary changes, vaginal bleeding or discharge, stress, anxiety, or depression. Vital signs are as follows: BP: 110/70; HR: 72; Temp: 98.7° F; RR: 12 O_2 100%; Wt: 145 lb; Ht: 5'7"; BMI: 24.

Physical exam reveals a healthy, well-nourished

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female in no acute distress. A complete physical exam from head to toe does not reveal any abnormality. Pelvic exam is normal, but breast exam reveals left breast tenderness and drops of milky discharge from the left nipple upon palpation.

"Symptoms in premenopausal women may include amenorrhea, infertility, oligomenorrhea, headache, breast tenderness, and galactorrhea."

Testing

A pregnancy test was ordered in office; it was negative. At that point, the differential diagnosis included prolactinoma, hypothyroidism, polycystic ovarian disease, and extra-uterine pregnancy. Additional testing was performed to further narrow the differential and included prolactin level, TSH and Free T4, FSH and LH, and B-HCG.

Results

Patient's lab results 2 days later showed an increased prolactin level of 31. She was referred to an endocrinologist, who obtained a brain MRI confirming the diagnosis of prolactinoma. In the subsequent visit with the endocrinologist, patient was started on bromocriptine, which reduced her prolactin to normal levels, resolving all of her symptoms.

PROLACTINOMA

Prolactin is a hormone produced exclusively by lactotroph cells of the anterior pituitary gland. Its hypersecretion is caused by factors directly influencing the lactotroph cells. The upper normal level of serum prolactin is 20 ng/mL. Hyperprolactinemia can be the result of physiologic or pathological causes.[1] Pregnancy can raise the prolactin level to 600 ng/mL at term.[1] Stress, physiological or psychological, can also increase the prolactin levels.[1] Nipple stimulation or sucking by newborns can stimulate the lactotroph cells as well.[1] Pathological causes include prolactinoma, which are benign tumors causing extremely high prolactin levels of even up to 50,000 ng/mL.[2] Prolactinoma account for approximately 30% to 40% of all clinically recognized pituitary adenomas.[3] The diagnosis is made more frequently in women than men, mostly between ages 20 and 40.[3]

A prolactinoma ≥1 cm in size is a macroadenoma; those <1 cm are considered microadenomas.[7] The amount of prolactin secretion is proportional to tumor size.[7]

Thyrotropin-releasing hormone (TRH), from the hypothalamus, has positive feedback on lactotroph cells, causing an increase in prolactin levels.[5] Although in most cases of hypothyroidism the basal serum prolactin concentrations are normal, a hypothyroid individual will have increased TRH levels which could increase prolactin levels.[5] Once hypothyroidism is corrected, the serum prolactin levels return to normal values.[6]

Presentation

Hyperprolactinemia causes hypogonadism in premenopausal women and in men.[13] In premenopausal individuals, the symptoms may include amenorrhea, infertility, oligomenorrhea, headache, breast tenderness, and galactorrhea.[13] Hyperprolactinemia accounts for 10% to 20% of cases of amenorrhea, caused by inhibiting gonadotropin-releasing hormone (GnRH).[14] Postmenopausal women by definition are already hypogonadal, so hyperprolactinemia does not change that situation; hyperprolactinemia in postmenopausal women is recognized if the lactotroph adenoma becomes too large, causing headache or vision changes, or may be identified accidently on an MRI performed for other reasons. In men, hyperprolactinemia causes decreased libido, impotence, infertility, gynecomastia, and (rarely) galactorrhea.[15]

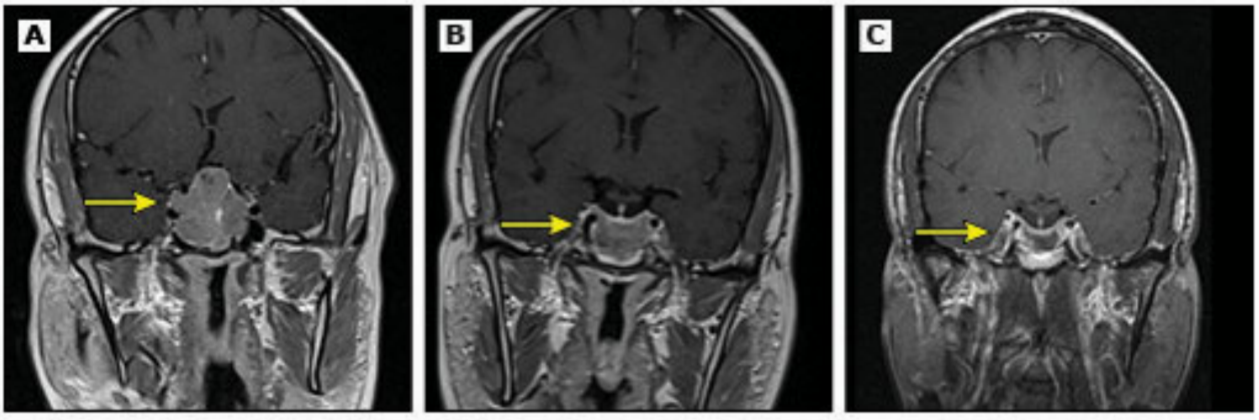
Diagnosis

The diagnosis of hyperprolactinemia is made when the serum prolactin concentration is above the normal value of 20 ng/mL. Caution should be exercised in interpreting serum prolactin concentration between 20 and 200 ng/mL due to wide verity of etiologies.[16] MRI of the brain should be performed with increased prolactin levels to look for a mass lesion in the hypothalamic-pituitary region, unless there is an alternative explanation.[4] If a brain mass is found on brain MRI, other hormones of the pituitary gland should also be evaluated. If the MRI is normal, and there are no obvious causes of hyperprolactinemia, the diagnosis of idiopathic hyperprolactinemia is made. Idiopathic hyperprolactinemia could be caused by very small adenomas that are not detectable on imaging studies.[16]

Treatment

Prolactinomas are more amenable to pharmacological treatment than any other pituitary adenomas. This is because of the availability of dopamine agonist drugs,

Figure 1.



A 37-year-old man with a diagnosis of prolactinoma A) at initial presentation; B) after 2 months of treatment with cabergoline; and C) after 12 months of treatment.[4]

which decrease the production of prolactin and reduce the adenoma's size.

There are two indications why a patient with hyperprolactinemia needs to be treated: the presence of neurological symptoms due to mass effect and the presence of hypogonadism.[8] The first-line treatment of hyperprolactinemia of any cause, including prolactinoma, is dopamine agonists.[9] Cabergoline is the first drug of choice and bromocriptine is the second line of treatment.[10] In patients with visual disturbance due to prolactinoma, vision usually begins to improve within days after initiation of therapy.[11] (See **Figure 1**, which tracks a 37-year-old man with a diagnosis of prolactinoma through a course of treatment.)[12]

"Diagnosis of hyperprolactinemia is made when serum prolactin concentration is above the normal value of 20 ng/mL."

Conclusion

Prolactinomas are an important and relatively common cause of amenorrhea, and should be considered in the differential in the nongravid female. Males with sexual dysfunction should also be considered for prolactinoma. Measurement of serum prolactin levels is an easy initial screen. An MRI is the study of choice when hyperprolactinemia is present. Most prolactinomas are amenable to treatment. While patients are usually followed by their primary care physician or gynecologist, amenorrhea is not an uncommon presentation in urgent care. Thus, a basic understanding of the differential and initial testing is useful in our setting. ■

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