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Approach to the Patient with Persistent Hyperprolactinemia and Negative Sellar Imaging

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Hyperprolactinemia is a common cause of menstrual disturbances affecting young women. There is a diversity of causes, from physiological, such as pregnancy, to pharmacological and pathological, such as hypothyroidism. Renal and hepatic failure, intercostal nerve stimulation by trauma or surgery, prolactinomas, other tumors in the hypothalamus-pituitary region, as well as macroprolactinemia can also be considered. Identifying the correct cause is important to establish the correct treatment. Should all these causes be ruled out and pituitary imaging revealed as negative, idiopathic hyperprolactinemia is therefore diagnosed.

In symptomatic patients, treatment with dopaminergic agonists is indicated. As for the asymptomatic hyperprolactinemic individuals, macroprolactinemia should be screened, and once it is detected, there is no need for pituitary imaging study or for dopaminergic agonist use. (*J Clin Endocrinol Metab* 97: 2211–2216, 2012)

Case Report

A 33-yr-old woman had her serum prolactin (PRL) assayed during a routine gynecological evaluation, and the result was 147 ng/ml (normal range, 2.5–15 ng/ml; immunofluorometric assay, Wallac AutoDelfia, PerkinElmer Life Sciences, Boston, MA). After menarche at 15 yr, she presented regular menses and no galactorrhea or libido disturbances.

She was on oral contraceptive pills until she was 28 yr old, when she stopped contraception to try pregnancy for 2 yr without success. She denied using any potential drug that could induce hyperprolactinemia. Transvaginal ultrasound and sellar magnetic resonance imaging (MRI) (Fig. 1) were performed, with no abnormalities detected. To restore her fertility, treatment for hyperprolactinemia was suggested, and she was then referred to our institution.

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Upon completion of this educational activity, participants should be able to:

- Identify the etiology of hyperprolactinemia amongst physiological, pharmacological and pathological as hypothyroidism, renal and hepatic failure, intercostal nerves stimulation, prolactinomas and other tumors of the sellar region.
- Make the clinical diagnosis in order to direct proper laboratory and imaging diagnosis when indicated.

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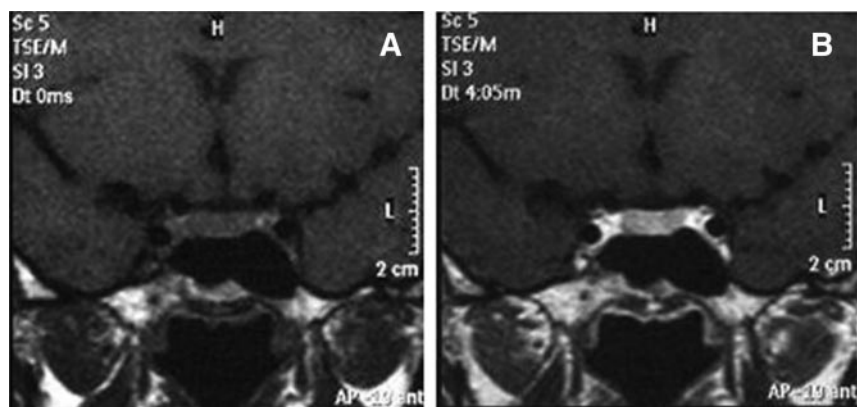


FIG. 1. Sellar MRI depicting normal pituitary gland I; coronal views without (A) and with (B) gadolinium enhancement.

Background

Hyperprolactinemia, defined by a high level of serum PRL above the standard upper limit of normal range, is the most common hypothalamus-pituitary dysfunction. In nonpregnant and non-nursing women, the clinical picture mimics the puerperal period, characterized by irregular menses or amenorrhea, galactorrhea, infertility, and a decrease of libido. In men, hypogonadism, infertility, and libido impairment could be found. Additionally, patients with hyperprolactinemia can also exhibit hypopituitarism, visual impairment, and headache (1) due to an expanding mass.

Therefore, nonphysiological hyperprolactinemia must be recognized and treated. Indications for measuring se-

rum PRL include galactorrhea, irregular menses, infertility, and pituitary tumors.

Causes of hyperprolactinemia are listed on Table 1. Nevertheless, the aim of this article is to point out and discuss only the differential diagnosis of hyperprolactinemia associated with negative imaging of the hypothalamus-pituitary region.

Many causes of hyperprolactinemia can be suspected during anamnesis, such as drug use, renal or hepatic failure, and hypothyroidism. In patients with suspicious drug-induced hyperprolactinemia, it is recommended to perform new PRL

evaluation after discontinuing medication for at least 3 to 4 d.

When drug withdrawal is unsafe, a MRI should be taken to rule out a sellar mass. If drug-induced hyperprolactinemia is confirmed, try to switch to an alternative medication.

The dopamine antagonists like risperidone, haloperidol, and sulpiride are the main class of psychoactive drugs leading to hyperprolactinemia, and they should be discontinued only by psychiatrists. If it is not possible to switch or withdraw the drug, hormonal replacement for hypogonadism is indicated, because dopamine agonists (DA) may oppose the beneficial antagonism of antipsychotic drugs (2). Aripiprazole, ziprasidone, and olanzapine are atypical antipsychotic drugs that do not cause hyperprolactinemia. Drug mechanisms that can cause hyperprolactinemia are: antagonistic effect on D2 receptors (antipsychotic drugs and gastrointestinal drugs as metoclopramide and domperidone), hypothalamic dopamine blockage (verapamil), and inhibition of enzyme that converts L-dopa to dopamine by α -methyl dopa (2).

Decreased PRL clearance and reduced inhibitory dopaminergic tonus by uremia are responsible for hyperprolactinemia, which is found in up to 30% of the cases in patients suffering from renal failure. Serum PRL levels depend on renal failure degree, and they can only return to normal status after a successful kidney transplant (3, 4). Marked hyperprolactinemia can be found in patients with renal failure using drugs that could induce hyperprolactinemia (5). Yavuz *et al.* (6) did not find macroprolactinemia in patients affected with renal failure. Hyperprolactinemia is defined by a high level of serum PRL, above the standard upper limit, and obtained without excessive venipuncture stress. Macroprolactinemia is defined when there is a prevalence of macroprolactin as the major circulating PRL isoform, which will be detailed below in this section.

About 60% of cirrhotic patients accuse the presence of mild hyperprolactinemia (7), without correlation between

TABLE 1. Causes of hyperprolactinemia

Physiological: pregnancy and lactation, physical activity, mammary stimulation
Pharmacological: antipsychotics, especially neuroleptics, antidepressants, opiates, and cocaine; antihypertensive medications (verapamil, methyl dopa, reserpine); gastrointestinal medications (metoclopramide, domperidone); protease inhibitors; and estrogens
Associated to general diseases: renal failure, liver failure
Associated to endocrine diseases
Hypothyroidism
PCOS
Pituitary adenomas
Prolactinomas
Mixed secretion of PRL/GH
Cushing's disease, Nelson's syndrome, Addison's disease
Pituitary stalk disconnection
Nonpituitary tumors: craniopharyngioma, meningioma, germinoma, metastasis
Pituitary tumors other than prolactinomas
Infiltrative lesions: sarcoidosis, histiocytosis, lymphomas, hypophysitis
Postoperative, radiotherapy
Intrasellar arachnoidocele ("empty sella")
Breast or thoracic surgery, chest wall trauma (intercostal nerves stimulation)
Macroprolactinemia
Idiopathic

PRL levels and the severity of liver failure. Etiopathogenesis is unknown (8).

The major mechanism causing hyperprolactinemia in primary hypothyroidism is an increase in the levels of TRH, which stimulates PRL secretion (9).

Moreover, other mechanisms such as reduced PRL clearance, decreased sensitivity to the suppressant effect of dopamine on PRL synthesis, and decreased circulating thyroid hormone levels could be involved. Hyperprolactinemia was found in up to 40% of patients with clinical hypothyroidism. Interesting enough, Hekimsoy *et al.* (10) found hyperprolactinemia in 22% of patients with subclinical hypothyroidism (defined by increased TSH with normal serum thyroid hormones). Serum PRL levels return to normal after the replacement of L-thyroxine. Concerning the clinical picture, Raber *et al.* (11) did not find differences in the prevalence of irregular menses or galactorrhea in 1003 hypothyroid patients with or without hyperprolactinemia.

Previous studies observed hyperprolactinemia in up to 30% of patients suffering from polycystic ovary syndrome (PCOS), and the influence of estrogen levels and dopaminergic tonus reduction were referred to as possible causes (12). More recently, a physiopathological link between PRL and PCOS was not confirmed, and their relationship was considered a fortuitous association (13, 14).

Nipple stimulation in nonpregnant women also increases the level of PRL due to a neurogenic reflex, an afferent pathway independent from dopaminergic neurons. Chest wall injury such as mechanical trauma, burns, surgery, and herpes zoster of thoracic dermatomes can also cause hyperprolactinemia (15). Reported cases of galactorrhea associated with hyperprolactinemia were also described after breast augmentation surgery and nipple piercing (16, 17). Breast stimulation, such as clinical examination (18), ultrasound, or mammography, has only a minimal effect on serum PRL levels in normal women (19).

Macroprolactinemia is defined by the presence of more than 50% of serum PRL as macroprolactin (or big-big-prolactin), an isoform of high molecular weight and low biological activity (20). Macroprolactin causes hyperprolactinemia as a consequence of low renal PRL clearance and a decreased stimulation of dopaminergic tonus.

Macroprolactinemia is responsible for hyperprolactinemia in 10 to 46% of the cases (21), and it should be screened in the following situations: individuals with high PRL levels but no indications of clinical symptoms, atypical clinical picture, conflicting PRL results in distinct assays, and delayed decline of serum PRL levels with the usual doses of DA (22). If monomeric prolactin level is also high, clinical picture can be present, despite the presence of macroprolactinemia (23). Screening by precipitation with polyethylene glycol (PEG)

is widely performed due to its low cost and practicability. The detection of macroprolactinemia via PEG precipitation was validated against gel filtration chromatography, the “gold standard” method to evaluate PRL isoforms. Recovery rates lower than 30 to 50% of total serum PRL levels in the supernatant are compatible with macroprolactinemia (23). Prolactin level measurement in macroprolactinemia serum depends on the PRL assay used. In one study, nine different immunoassays were tested in 10 sera containing macroprolactinemia, and serum PRL level differences ranged from 2.3 to 7.8-fold (24).

Although macroprolactin is, in general, composed of a complex formed with an IgG and a monomeric PRL (25), macroprolactinemia does not seem to be linked to autoimmune diseases (26). Macroprolactin levels remain stable for a long time. Vallette-Kasic *et al.* (27) evaluated 106 macroprolactinemic individuals. Prolactin levels ranged from 20 to 663 ng/ml, and levels below 100 ng/ml are responsible for more than 90% of cases. Although PRL levels remained almost unchanged, large individual variations occurred. Seven women became pregnant during follow-up, and deliveries were uneventful. These data confirmed macroprolactinemia as a benign condition in terms of fertility. Infertility originating from other causes may coincidentally occur in macroprolactinemic women (28).

If the aforementioned causes were ruled out, hyperprolactinemia should be defined as idiopathic. Factors like the lack of sensitivity of imaging methods, such as a plain sellar x-ray machine and computerized tomography scan in the past, as well as the evidence of a hard-to-detect (even for MRI standards) presence of microprolactinoma are some possible explanations for a symptomatic patient with idiopathic hyperprolactinemia (29). Alternatively, De Bellis *et al.* (30) found a high prevalence of antipituitary antibodies (APA) in 25.7% of patients with idiopathic hyperprolactinemia, whereas all patients with microprolactinomas and normal controls were negative for APA. Among 17 patients positive for APA, six had other pituitary deficiencies. These findings pointed to a pituitary autoimmune involvement causing hyperprolactinemia, and it must be suspected in patients with idiopathic hyperprolactinemia and personal or familial history of autoimmune disease. However, no other studies reproduced these findings, and APA testing is not commercially available.

Diagnostic and Therapeutic Strategies

Before proceeding with the imaging investigation, pregnancy, hypothyroidism, renal or hepatic failure, and drugs

must be ruled out as causes of hyperprolactinemia because pituitary incidentaloma can be found in 10% of sellar MRI in normal individuals, becoming, therefore, a diagnostic pitfall (31). In asymptomatic patients, macroprolactinemia should be excluded, and if positive, sellar MRI is not indicated (32). As a matter of fact, prolactinomas could be associated to macroprolactinemia, but in this case patients are usually symptomatic, and they would need an imaging study (33).

Dynamic testing for PRL (with TRH and dopamine antagonist drugs) is not useful in differential diagnosis of hyperprolactinemia, and it is not recommended by The Endocrine Society's guidelines (34).

Stress could increase PRL secretion; therefore, levels that are just outside the normal range should be repeated (35). Muneyyirci *et al.* (36) found that nearly 30% of hyperprolactinemia was stress related in 70 women with hyperprolactinemia, and Vieira *et al.* (37) described a similar percentage: 25.5% in 157 patients. If mild hyperprolactinemia persists in an asymptomatic patient without macroprolactinemia, PRL evaluation should be repeated after 30 min of rest. Figure 2 shows an algorithm with diagnostic strategies.

Treatment is indicated in symptomatic patients with idiopathic hyperprolactinemia. DA are the therapy of choice because they promote serum PRL normalization, restore hypothalamus-pituitary-gonadal axis function, and abrogate galactorrhea. Among DA, cabergoline is the first choice due to its efficacy and tolerability (38), although data about its safety during pregnancy is far less published compared with bromocriptine (34). Although this drug was related to cardiac valve disease in patients

with Parkinson's disease (39, 40), its effect in hyperprolactinemic patients is still controversial (41). The necessity of continuous treatment with DA should be reevaluated because serum PRL levels may remain normal after drug withdrawal. In a meta-analysis performed by Dekkers *et al.* (42), 32% of patients with idiopathic hyperprolactinemia kept normal PRL levels after DA discontinuation. This finding may reflect the natural history of idiopathic hyperprolactinemia; as one study has shown, serum PRL levels returned to normal without any treatment in one third of patients (43). Therefore, in patients who attained normoprolactinemia, treatment with DA should be periodically discontinued according to The Endocrine Society's clinical guidelines for diagnosis and treatment of hyperprolactinemia (34).

Controversies and Areas of Uncertainty

The maintenance of DA during menopause is debatable concerning two issues: pituitary tumor development and cancer risk. Following up on patients with idiopathic hyperprolactinemia without treatment, analysis showed that microprolactinomas appeared in only 10% of cases and no macroadenoma was reported in such patients (43). Therefore, the need of continuous treatment to prevent the growth of prolactinomas seems to be unnecessary. Concerning the follow-up imaging, the only potential conditions in which we suggest performing a new sellar MRI are the increase in PRL levels during DA treatment or marked PRL elevation above pretreatment levels after DA discontinuation.

As far as cancer risk is concerned, and although experimental evidence indicates that PRL might play a role in tumorigenesis of several cancers (44), the influence of hyperprolactinemia in human beings is controversial. In a prospective nested case-control study within the Nurse's Health Study cohort, serum PRL levels were associated with a modestly increased risk of breast cancer, especially in breast cancer expressing estrogen/progesterone receptors (45). More recently, a cohort of hyperprolactinemic hospitalized patients and outpatients with prolactinomas was performed, and an overall increased risk of developing cancer was found, notably in hematopoietic cancer in females and upper gastrointestinal cancer in both genders, without evidence of an increased risk of breast cancer in women (46). To date, there is no indication of treating hyperprolactinemia intended to prevent cancer development.

Concerning macroprolactinemia, screening is controversial. Some authors indicate screening for macroprolactinemia in all hyperprolactinemic individuals to

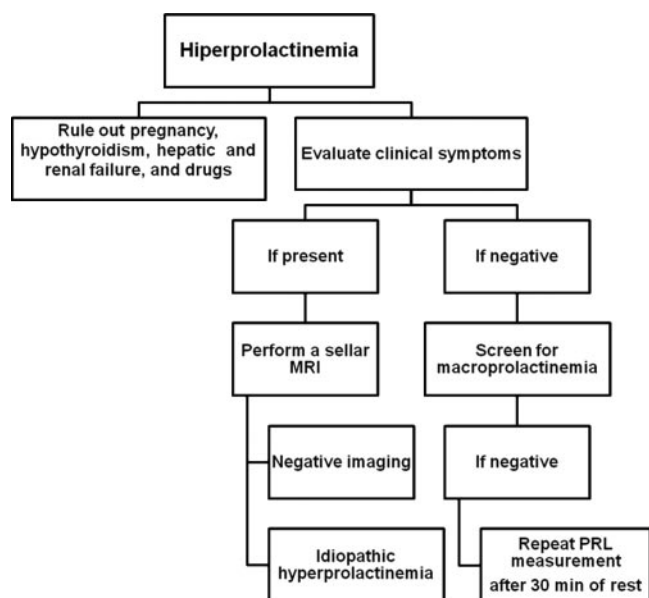


FIG. 2. Algorithm for diagnostic strategies in hyperprolactinemia with negative image.

avoid unnecessary pituitary imaging and treatment (23), whereas others suggest this procedure only if discrepant findings were observed regarding clinical presentation or biological follow-up (27). In our opinion, the macroprolactinemia “epidemics” could be avoided by performing PRL assessment only in the presence of hyperprolactinemia-related symptoms.

Does macroprolactin have any harm? Anafroglu *et al.* (47) studied platelet activation looking at P-selectin expression in hyperprolactinemic, macroprolactinemic, and normoprolactinemic subjects, matched regarding blood pressure, plasma lipids, waist circumference, and insulin sensitivity status. Platelet activation was greater in hyperprolactinemic and macroprolactinemic patients. Reuwer *et al.* (48) recently demonstrated the presence of PRL receptor in macrophages from atherosclerotic plaque, and they hypothesized about a probable PRL role in the local inflammatory response in the atherosclerotic plaque. Nevertheless, the linkage of macroprolactinemia and atherosclerotic disorders is still controversial.

Returning to the Patient

Because our patient had regular menses and no galactorrhea, progesterone assay was performed during the luteal phase, and PRL was then reassessed. Serum PRL level reached 112 ng/ml and progesterone, 4.3 ng/ml (normal range, 3.6–21.7 ng/ml), which is consistent with an ovulatory cycle. Due to the dissociation between laboratory finding and clinical picture, screening of macroprolactinemia was performed by precipitation with PEG and produced a positive result: only 8% of total serum PRL was recovered in the supernatant (7.2 ng/ml). We also performed thyroid, renal, and hepatic assessments, which were normal.

Hyperprolactinemia due to macroprolactinemia was diagnosed, and no specific treatment for hyperprolactinemia was indicated. The cause of the patient’s infertility should be further investigated.

Conclusions

In patients with persistent hyperprolactinemia, pregnancy, hypothyroidism, renal or hepatic failure, drugs and macroprolactinemia should be ruled out before performing a sellar MRI. If no previous causes were identified and the patient is symptomatic, pituitary imaging should be done. If normal, idiopathic hyperprolactinemia is diagnosed, and DA treatment is indicated.

Macroprolactinemia is present in up to 46% of hyperprolactinemic individuals and should be screened in

asymptomatic individuals with high PRL levels. In the absence of symptoms, neither pituitary study imaging nor medical treatment is indicated. Macroprolactinemic patients could present hyperprolactinemia-related symptoms when serum monomeric PRL level is outside the normal range, as in cases associated with prolactinoma, for instance. In this situation, treatment with DA is recommended. On the other hand, a macroprolactinemic patient with normal monomeric PRL levels should be correctly evaluated for irregular menses or infertility because other causes for these symptoms could coexist with macroprolactinemia, and the use of DA is not recommended.

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