

Persistent Idiopathic Prolactin Elevation Merits Macroprolactin Estimation: A Case Report and Review of Literature

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ABSTRACT

The prevalence of hyperprolactinemia ranges from about 0.4% in an unselected adult population to as high as 9%–17% in women with reproductive disorders. It may cause infertility in about 11% of the oligospermic males. Rarely, the cause of persistently elevated prolactin remains obscure even after thorough work up. Macroprolactinemia is biologically inactive, high-molecular-weight form of prolactin resulting from its binding to immunoglobulin G, causing a decrease in its clearance. We report the case of a 35-year-old female, detected to have hyperprolactinemia on multiple tests, during routine work up for primary infertility. Secondary causes for the same were ruled out. A magnetic resonance imaging (MRI) of the brain excluded a prolactinoma. This prompted an estimation of prolactin levels after polyethylene glycol precipitation which showed a decrease to 5.58 ng/mL, with <40% recovery, confirming the presence of macroprolactin. Thus, persistently elevated prolactin levels in the background of negative neurological imaging necessitate the estimation of macroprolactin.

KEYWORDS: *Hyperprolactinemia, macroprolactin, polyethylene glycol precipitation*

INTRODUCTION

Historically first described by Whittaker, macroprolactin or “big, big prolactin” is a biologically inactive, high-molecular-weight form of prolactin that is detected to varying degrees by different prolactin immunoassays.^[1] There are estimates to suggest that the presence of macroprolactin leads to misdiagnosis in as many as 10% of reported cases of biochemical hyperprolactinemia.^[2] Occasionally, persistent elevation in prolactin levels cannot be explained even after a thorough clinical, hormonal, and neuro-radiological workup.^[2,3] This warrants estimation of macroprolactin. Here, we present the case of a 35-year-old female with primary infertility and raised serum prolactin levels, which after a thorough work up revealed the presence of macroprolactin.

CASE REPORT

A 35-year-old female undergoing workup for primary infertility was referred to the endocrinology outpatient

department for evaluation of raised serum prolactin levels. She had been married for 7 years and had not conceived a child. She had a history of oligomenorrhoea for the past 10 years and was initiated on cyclical estrogen-progesterone pills for regularization of her menstrual cycles. There were no headache, nausea, vomiting, or problems relating to visual acuity and field of vision. She denied the intake of any medications including proton pump inhibitors, antipsychotics, or prokinetic agents that could potentially elevate prolactin levels. There was no history to suggest hypothyroidism, liver, or renal dysfunction. On clinical examination, she was obese with a body mass index (BMI) of 36 kg/m². There were no physical stigmata of Cushing syndrome or acromegaly. There were no features of virilization,

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hirsutism, or galactorrhea. Local examination did not reveal the presence of any chest wall lesions. Her visual fields assessed by the confrontation method were normal.

The prolactin levels repeated on multiple occasions were found to be elevated with values of 135.5 ng/mL, 127 ng/mL, and 107.8 ng/mL (Normal range in females: 5–25 ng/mL) Other investigations are shown in Table 1. In view of persistently elevated prolactin levels in the background of primary infertility, she underwent an MRI of the brain with pituitary focused images which failed to reveal any focal mass lesions [Figure 1].

As the serum prolactin level was elevated in isolation and clinical and laboratory evaluation to suggest secondary causes were unyielding, it was decided to proceed with a polyethylene glycol (PEG) precipitation test. A repeat serum sample was obtained in the nonfasting state and prolactin was estimated after pretreatment of the sample with polyethylene glycol. This showed the prolactin levels to be 5.58 ng/mL, with a recovery of <40%. This confirmed the hyperprolactinemia to be secondary to the presence of macroprolactin, and the patient was reassured.

DISCUSSION

Hyperprolactinemia is the most common endocrine disorder of the hypothalamopituitary axis. It is more common in women. Its prevalence ranges from about 0.4% in an unselected adult population to as high as 9%–17% in women with reproductive disorders.^[4] It may also cause infertility in about 11% of the oligospermic males.^[5] Its clinical manifestations include hypogonadism, which in females is characterized by infertility, amenorrhea or oligomenorrhea, and galactorrhea. Hyperprolactinemia secondary to a prolactin-producing pituitary adenoma may produce symptoms related to tumor mass in the form of headache, visual disturbances, and involvement of the other pituitary axes. The diagnostic process of a prolactinoma involves the exclusion of other physiologic and pharmacologic causes of prolactin elevation as shown in

Table 1: Laboratory investigations

Test (reference range)	Value
Hemoglobin (12-15 g/dL)	13.1
TSH (0.3-4.5 mIU/L)	4.9
Free T4 (0.8 - 2.0 ng/dL)	1.3
LH (1.1-11.6 mIU/mL; follicular phase)	8.36
FSH (2.8-11.3 mIU/mL; follicular phase)	6.05
Creatinine (0.7-1.4 mg/dL)	0.6

TSH=Thyroid-stimulating hormone, LH=Luteinizing hormone, FSH=Follicle-stimulating hormone, T4=Thyroxine

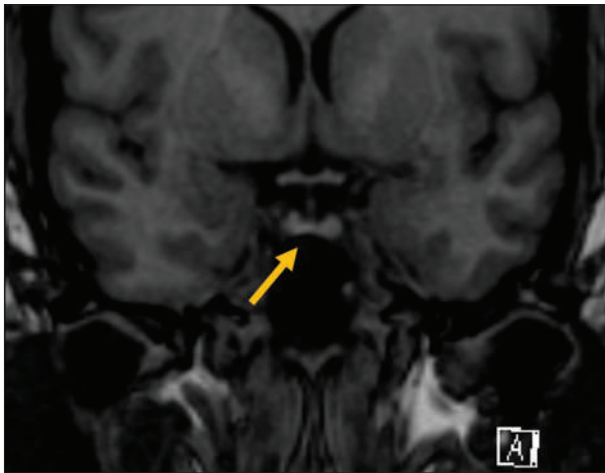
Table 2.^[6] Typically, the normal value of serum prolactin in the authors' center ranges from 1.9 to 25 ng/mL in females and 2.5–17 ng/mL in males (Chemiluminescent Immuno-assay; Atellica Siemens, Benedict Avenue, Tarrytown, NY, USA). Prolactin values up to 200 ng/mL may be related to the intake of certain drugs or a microprolactinoma; levels >200 ng/mL are usually due to a prolactin-secreting pituitary macroadenoma.^[7]

Prolactin is synthesized as a prehormone with a molecular weight of 26 kDa. Cleavage of this prehormone leads to the formation of the 23 kDa “little prolactin,” the monomeric form which is also the major circulatory and immunologically active form of prolactin. It should be noted, however, that human prolactin is heterogeneous with respect to its molecular size. “Big prolactin” has a molecular weight of 50 kDa and macroprolactin, which is “big, big prolactin” has a molecular weight >150 kDa, owing to its being complexed with anti-prolactin antibodies of the immunoglobulin G (IgG) isotype. Prolactin in this complexed form is cleared slowly the clearance rate being similar to that of IgG which can result in apparent hyperprolactinemia. By virtue of its high molecular mass, macroprolactin is confined to the intravascular space and is unable to cross the capillary endothelium to its target tissues, thus rendering it biologically inactive though immunoreactive. As a consequence, such individuals exhibit biochemical hyperprolactinemia but little, if any, evidence of the usual clinical consequences of true hyperprolactinemia. Although the prevalence of macroprolactin is estimated to account for 16%–50% of cases previously diagnosed to have idiopathic hyperprolactinemia, the source of these antiprolactin antibodies is unclear. It is speculated that posttranslational modification of prolactin in the form of glycosylation, phosphorylation, deamidation, or sulfation, may result in the formation of neoepitopes, which may result in antibody formation if the immune system is intolerant to these epitopes.^[6]

Although gel filtration chromatography is considered to be the gold standard reference assay in the diagnosis of macroprolactin, this is expensive and labor intensive.^[8] Laboratory diagnosis of macroprolactin is carried out by PEG precipitation. This method employs pretreatment and incubation of the sera with polyethylene glycol followed by centrifugation. After centrifugation, the unprecipitated prolactin in the supernatant is measured. The PEG-precipitable PRL (%), which represents the amount of macroprolactin, is calculated as follows: (total prolactin-free prolactin)/total prolactin × 100. PEG-precipitation ratio >60% (recovery <40%) is used as the cut-off value for the diagnosis of macroprolactinemia. Recovery rates of prolactin that

Table 2: Causes of hyperprolactinemia

Physiological causes	
Pregnancy, breast stimulation, stress, pain, coitus, excessive physical training	
Pathological causes	
Source	Aetiology
Pituitary disease	Prolactinoma, growth hormone-producing pituitary adenoma, nonfunctioning adenoma due to stalk effect, hypophysitis, infiltrative disorders, metastases
Hypothalamic disease	Tumors such as craniopharyngioma, dysgerminoma, meningioma, cranial irradiation, infiltrative disorders such as histiocytosis, sarcoidosis
Associated systemic diseases	Renal failure, primary hypothyroidism, adrenal insufficiency, polycystic ovary syndrome, renal failure, cirrhosis, pseudocystitis, epileptic seizures
Neurogenic causes	Chest wall lesions - Herpes zoster, breast surgery, burns, thoracotomy, trauma, cervical ependymoma
Medications	Antipsychotics (risperidone, amisulpride, and quetiapine), prokinetics (metoclopramide, domperidone), anticonvulsants (phenytoin), antihypertensives (verapamil, reserpine, alpha methyl dopa, labetalol), anti-depressants (amitriptyline, desipramine, fluoxetine), estrogen
Analytical	Macroprolactin, heterophile antibodies, hook effect

**Figure 1:** Magnetic resonance imaging of the brain demonstrating normal-sized pituitary gland

is <40% is suggestive of the presence of macroprolactin, recovery of 40%–50% needs chromatographic work-up and >50% rules out macroprolactinemia.^[9] An algorithm for the diagnosis of macroprolactinemia^[10] is shown in Figure 2.

In the patient discussed above, there was persistent prolactin elevation in the range of 100–140 ng/mL. A thorough history with careful attention to the use of potential offending medications ruled out drugs and other physiological causes of hyperprolactinemia. Although she had complaints of irregular menstrual cycles, there was no galactorrhea. She had a BMI of 36 kg/m² with polycystic appearance of ovaries on sonogram, which was probably responsible for the menstrual irregularity. An MRI of the brain with pituitary-focused images performed to exclude the possibility of a pituitary adenoma was reported to be normal. This prompted the assessment of macroprolactin, the presence of which was confirmed on a PEG precipitation test, that yielded

a prolactin value of 5.58 ng/mL (PEG-precipitable prolactin was 95%, and recovery was 5%). The authors proceeded with an MRI of the brain as well as macroprolactin assessment for the reason that macroprolactinemia may rarely coexist with a pituitary macroadenoma.^[11] The primary infertility and menstrual irregularity in this patient were probably attributable to her obesity and polycystic ovary syndrome. This patient had received combined estrogen-progesterone pills for regularization of her menstrual cycles. Although about 12%–30% of women may develop minimal elevation of serum prolactin while on estrogen therapy,^[12] the hyperprolactinemia secondary to the presence of macroprolactin could not be attributed to contraceptive use. She was thus reassured and proceeded with further evaluation of infertility and the possibility of assisted reproductive techniques in planning conception.

Although macroprolactinemia usually lacks symptoms of oligomenorrhea and galactorrhea, previous studies have shown conflicting results. In a study by Taghavi *et al.* it was shown that out of 17 infertile women with hyperprolactinemia, 35% of them had macroprolactinemia. Of the patients with macroprolactinemia, about 33% had galactorrhea, 16% had oligomenorrhea and all had MRI findings of a normal pituitary gland.^[6] In another study by ValletteKasic *et al.*, out of 106 patients with macroprolactinemia, 61% had normal menstruation, and 54% did not have galactorrhea.^[13] Macroprolactinemia is often neglected in the differential diagnosis of idiopathic hyperprolactinemia. The diagnosis of idiopathic hyperprolactinemia is made when sustained hyperprolactinemia occurs in the absence of any identifiable cause of hyperprolactinemia, including the finding of a normal pituitary gland on an MRI of the brain. The simultaneous occurrence of the nonspecific

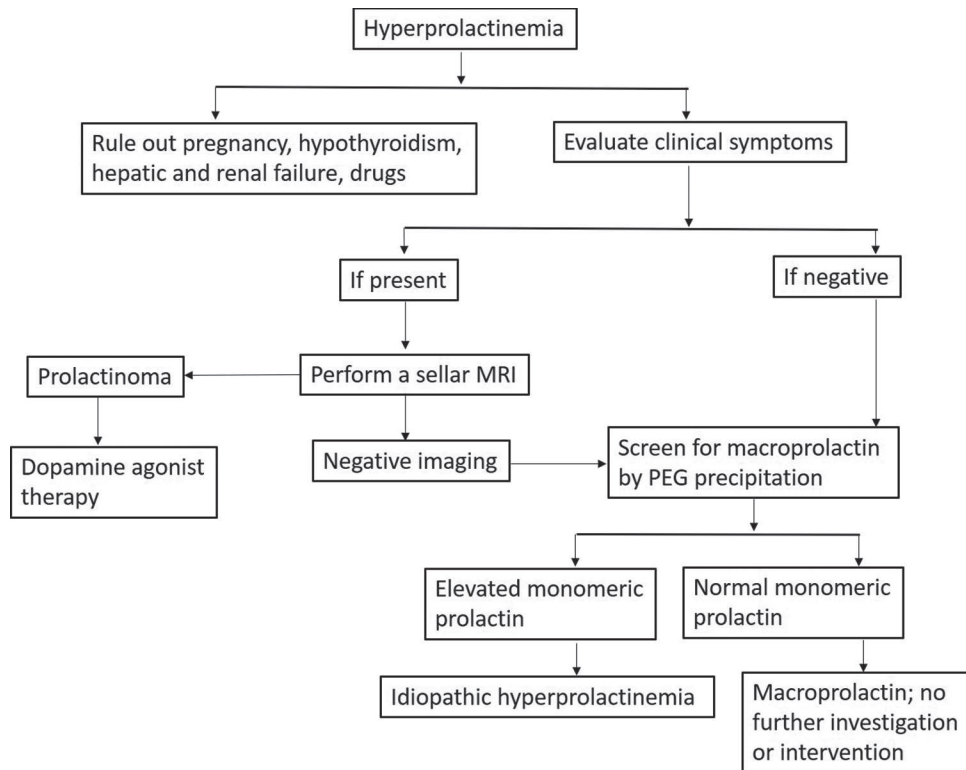


Figure 2: Algorithm for the diagnosis of macroprolactinemia

symptoms of hyperprolactinemia such as oligomenorrhea together with macroprolactinemia may cause clinical confusion as in the patient presented above. Macroprolactinemia is not known to require specific treatment although occasionally mild symptomatology might warrant a trial of dopamine agonist therapy.^[14]

CONCLUSION

Macroprolactin is a rare and obscure cause of prolactin elevation. Differentiation between the apparent benign clinical condition of macroprolactinemia where hyperprolactinemia is entirely explained by the presence of macroprolactin and true hyperprolactinemia, which requires therapy, is necessary to avoid misdiagnosis and erroneous management of patients.

Patient consent

Obtained.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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