

Primary Hypothyroidism Associated with Hyperprolactinemia and Pituitary Macroadenoma

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Abstract. Objective: Our purpose is to report a case of primary hypothyroidism associated with hyperprolactinemia and pituitary macroadenoma. **Background:** We present the case report, including detailed laboratory and radiological findings in a 28-year-old woman. In primary hypothyroidism there is hyperplasia of both thyrotrophs and lactotrophs as a response to TRH hypersecretion. The hyperplasia can result in significant enlargement of the pituitary gland and can be mistaken for a prolactin-secreting tumor. **Case:** We report the case of a female patient who presented with amenorrhea of 7-months duration and was found by her gynecologist to have elevated prolactin. The initial MRI showed a 1.7 cm pituitary mass which was treated initially by cabergoline. Due to the patient's noncompliance and lack of follow up, the patient remained on cabergoline for 6 months and did not do thyroid function tests. Finally, after 6 months, a follow up MRI showed no change in size of her pituitary mass. Also, blood tests showed profound hypothyroidism, and after 6 month of thyroid replacement therapy, the patient was euthyroid. A repeated MRI of the brain showed complete resolution of the pituitary mass. **Result:** This case emphasizes the importance of evaluation of thyroid function in cases of elevated prolactin and gonadal dysfunction. Despite a lack of the typical clinical presentation of hypothyroidism, resolution of the patient's symptoms and disappearance of her pituitary macroadenoma confirms the diagnosis. **Conclusion:** This case illustrates that primary hypothyroidism can present with amenorrhea and pituitary mass.

Keywords • Amenorrhea • Hyperprolactinemia • Hypothyroidism • Pituitary macroadenoma • Prolactin

Introduction

Prolactin is a pituitary-derived hormone that plays a pivotal role in a variety of reproductive functions. Prolactin negatively modulates the secretion of pituitary hormones responsible for gonadal function, including luteinizing hormone and follicle-stimulating hormone. An excess of prolactin, or hyperprolactinemia, is a commonly encountered clinical condition and is most commonly secreted in excess by pituitary adenoma. The patient usually presents with galactorrhea and gonadal dysfunction.

It is important to measure prolactin levels in all patients with unexplained primary or secondary amenorrhea. This was emphasized in some previous studies that showed that as many as 20% of patients

with hyperprolactinemia did not have galactorrhea nor any signs of pituitary dysfunction. Vilar et al. reported on 1234 patients with different etiologies of hyperprolactinemia, as well as the response of 388 patients with prolactinomas to dopamine agonists.^[1]

Vilar et al. found that 56.2% of patients had prolactinomas, 14.5% had drug-induced hyperprolactinemia, 9.3% had macroprolactinemia, 6.6% had non-functioning pituitary adenomas, 6.3% had primary hypothyroidism, 3.6% had idiopathic hyperprolactinemia, and 3.2% had acromegaly.^[1]

In men, the diagnosis of prolactin-secreting tumors is usually delayed until visual impairment or hypopituitarism appears. The reason is the male's initial signs of gonadal dysfunction. These signs, decreased libido and occasionally galactorrhea, are as-

sociated with prolactin excess are usually ignored.

There are many conditions associated with hyperprolactinemia. The most common causes are pregnancy, hypothalamo-pituitary disorders, drugs, and primary hypothyroidism.

With the development of the third generation TSH assay and the inclusion of thyroid function testing in annual blood screenings, hyperprolactinemia caused by primary hypothyroidism become less common. Primary hypothyroidism can be associated with diffuse pituitary enlargement, which reverses with appropriate thyroid hormone replacement therapy.^[2,3] However, primary hypothyroidism associated with a pituitary adenoma is extremely rare. Here, we report one such case.

Case Presentation

A 28-year-old female presented at her gynecologist's office with 7 months of amenorrhea in 2009. The patient initially complained also of occasional dizziness, but she did not have headaches, visual disturbances, or galactorrhea. The patient also denied diarrhea or constipation, as well as dry skin, hot and cold intolerance, weight change, and muscle cramps. She never had menstrual abnormalities prior to this episode. She had recently married. Her only medical history was knee surgery 10 years before. Her family history was positive for thyroid cancer, which her sister had. She never smoked or abused alcohol and was exercising regularly.

The initial laboratory work done by her gynecologist was negative for pregnancy, but it showed a prolactin level of 139 ng/mL. An MRI of the brain showed a 1.7 cm pituitary macro adenoma. The adenoma extended into the suprasellar region with indentation of the optic chiasm. Thyroid studies were also ordered but the patient did not follow up for reevaluation.

The gynecologist started the patient on 0.25 mg of cabergoline twice weekly. After 6 months, the patient came back with the same complaint of amenorrhea and a new symptom of "feeling cold all the time." Her prolactin level had decreased to 11.7 ng/mL and an MRI of the brain showed no change in the size of the pituitary adenoma. The patient was referred to an endocrinologist for possible surgery because of failure of the adenoma to shrink. Although no symptoms suggested hypothyroidism except cold

intolerance, blood tests showed a TSH of 562.5 μ U/mL, a FT₄ of 0.18 ng/dL, and a reference range IGF-1 level. Cabergoline was discontinued and the patient was started on levothyroxine. The dosage was titrated to 112 μ g daily.

The patient was closely followed afterwards and 6 months later, her prolactin level was 23.2 ng/mL and her periods were regular; TSH had decreased to 0.237 μ U/mL, her total T₃ was 127 ng/dL, and her FT₄ was 1.63 ng/dL. An MRI one year after she had started levothyroxine showed complete resolution of the pituitary adenoma.

Discussion

The hyperprolactinemia of hypothyroidism is related to several mechanisms. In response to the hypothyroid state, a compensatory increase in the discharge of TRH results in an increased stimulation of pituitary prolactin secretion. Hypothalamic thyrotropin releasing hormone (TRH) is a potent prolactin releasing factor, and it can cause thyrotroph hyperplasia.

The high level of TRH in severe primary hypothyroidism and the lack of T₄ feedback from the thyroid gland might cause proliferation and hypertrophy of both the pituitary gland's thyrotrophs and lactotrophs. The hypertrophy may mimic a pituitary adenoma. With proliferation of the thyrotrophs and lactotrophs in primary hypothyroidism, as illustrated in our case, there is a significant increase in TSH levels and only a moderate increase in the prolactin level.

In our patient, regression of her pituitary macroadenoma after treatment with levothyroxine confirmed the hypothesis of pituitary hyperplasia secondary to primary hypothyroidism. Cabergoline decreased her prolactin levels, but it did not decrease the size of the adenoma. This observation also supports the diagnosis of pituitary macroadenoma that was likely secondary to hypothyroidism.

Furthermore, prolactin elimination from the systemic circulation is reduced in severe hypothyroidism; this contributes to increased circulating prolactin concentrations. Primary hypothyroidism can be associated with diffuse pituitary enlargement, which will reverse with appropriate thyroid hormone replacement therapy.

In our case, primary hypothyroidism was not investigated and treated at the beginning of her care

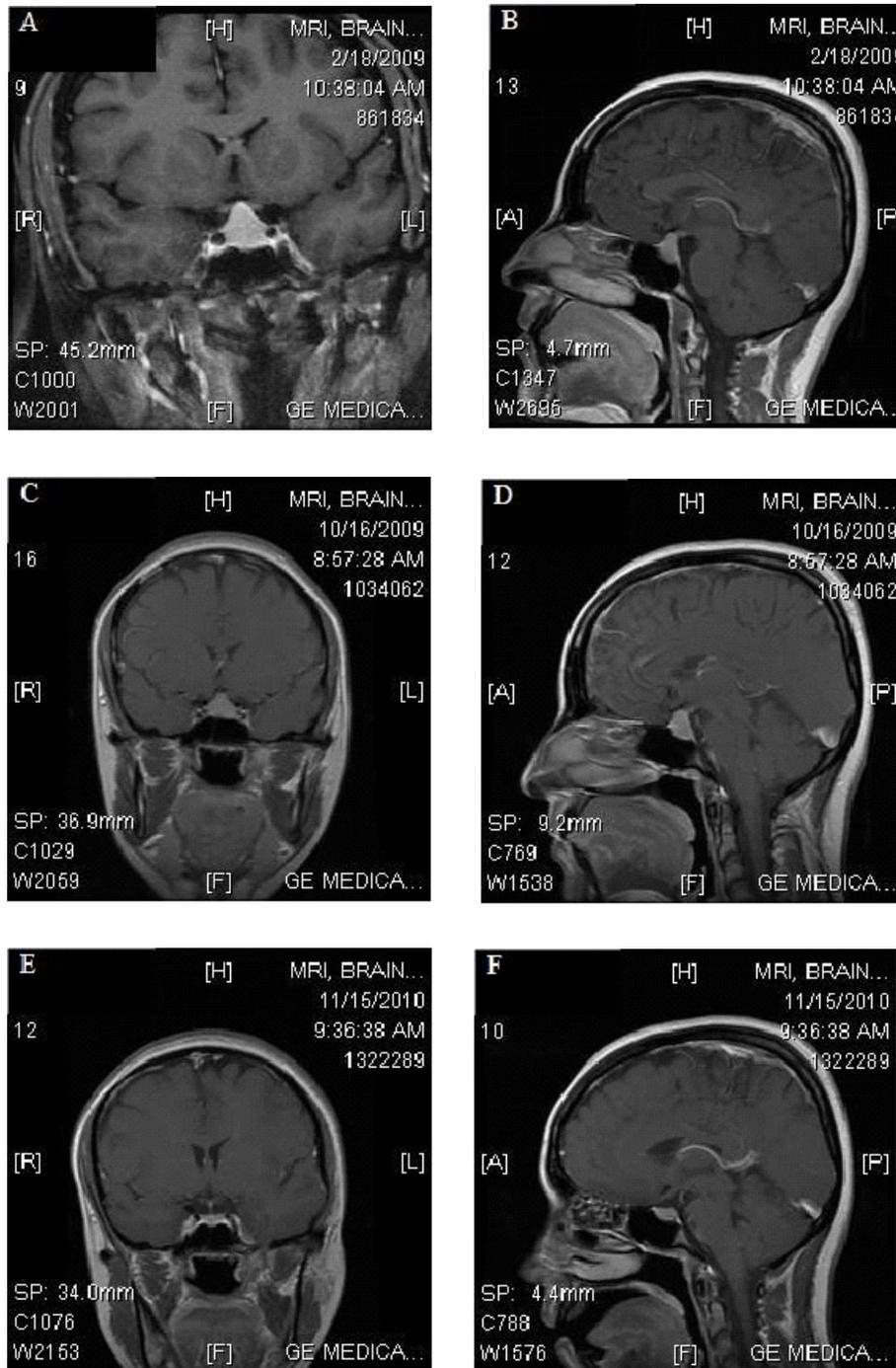


Figure. A and B: Coronal and sagittal post-gadolinium images show a 1.7 cm pituitary macroadenoma extending into the suprasellar region with indentation of the optic chiasm.

C and D: Coronal and sagittal post-gadolinium images show no difference in size of pituitary macroadenoma after 6 months of therapy with cabergoline

E and F: Coronal and sagittal post-gadolinium images show complete resolution of the pituitary mass after 6 months of thyroid hormone replacement therapy.

for three reasons: (1) the patient was relatively asymptomatic, (2) presented with a pituitary macroadenoma rather than a diffuse enlargement, and (3) was non-compliant.

This case illustrates the importance of doing

thyroid function tests in patients with hyperprolactinemia and pituitary macroadenoma. Doing so can avoid unnecessary pituitary surgery. However, surgical resection of a pituitary adenoma in primary hypothyroidism might still be necessary. In rare

cases, for example, paradoxical pressure symptoms and development of a visual field defect will occur in the first months of thyroid replacement therapy. These symptoms suggest that monitoring for pressure symptoms during the treatment is important.^[9]

TSH secreting pituitary tumors caused by primary hypothyroidism should be distinguished from true thyrotroph neoplasia that results in secondary hyperthyroidism. The appropriate therapeutic approach is completely different. TSH-omas are usually invasive macroadenomas and are known to be difficult to treat.^[6]

The timeline of growth and regression of pituitary adenomas in hypothyroidism after replacement therapy has been started has not been clearly established. Studies show that discontinuation of T₄ replacement in preparation for ¹³¹I therapy for only 3 weeks can cause significant enlargement of the pituitary gland.^[2] In one reported case, the patient had rapid regression of a pituitary adenoma after one week of T₄ replacement.^[7] In our case, the exact time course could not be established. However, regression of the pituitary macroadenoma after treatment with levothyroxine confirmed the hypothesis of pituitary hyperplasia secondary to primary hypothyroidism.

Conclusion

Patients with hypothyroidism do not always present with typical symptoms. Our case illustrates that primary hypothyroidism can present in amenorrhea and pituitary mass. This suggests the importance of thyroid function testing during the investigation of hyperprolactinemia and pituitary adenoma in order to avoid unnecessary surgery.

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