



Hyperprolactinemia associated with macroprolactinoma in a 17-year-old: A case report

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ABSTRACT

Hyperprolactinemia is a relatively common endocrine disorder. In women of reproductive age it may present as the amenorrhea-galactorrhea syndrome, but in milder forms also as menstrual abnormalities or infertility. Here we describe a 17-year-old girl previously treated with a combined oral contraceptive due to secondary amenorrhea. Hormonal tests showed hypogonadotropic hypogonadism with severe hyperprolactinemia (PRL concentration 1639 ng/ml). Further tests confirmed the presence of a pituitary macroadenoma. Cabergoline treatment was effective in the restoration of a spontaneous menstrual cycle and PRL normalization. In conclusion, clinicians should be aware of the diagnostic and therapeutic problems in the management of hyperprolactinemia.

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1. Introduction

Hyperprolactinemia is a state of elevated prolactin (PRL) concentrations in the blood. The well recognized upper limit for PRL in women is 25 ng/ml, but it may vary depending on the laboratory [1,2].

The etiology of hyperprolactinemia may be physiological (pregnancy, sleep, sexual intercourse), drug-induced (e.g., antipsychotic drugs) or pathological. The most common pathologies linked to hyperprolactinemia are a PRL-secreting pituitary adenoma (prolactinoma), and damage of the pituitary stalk caused by neoplasm, inflammatory disease or trauma.

The clinical presentation of hyperprolactinemia depends on its degree. The classical amenorrhea-galactorrhea syndrome is present when PRL serum concentrations are above 100 ng/ml. In milder forms, it may present as a luteal phase defect, poly- or oligomenorrhea and decreased libido [1,3]. Here we describe a case of severe hyperprolactinemia which had not been diagnosed correctly in the past, which is probably what led to complications.

Written informed consent was obtained from the patient and her parents for the publication of this case report and the accompanying images.

2. Case Report

A 17-year-old female presented with a complaint of lack of menses four months after the withdrawal of a combined oral contraceptive (COC). She also suffered from moderate headaches, which were tolerated without analgesic medication. She said she had not experienced hot flushes or other symptoms.

Her first menstrual period had occurred at the age of 13 and afterward she had regular menses for about two years. When she was 15 years old, her menses became irregular (40–60 days) and she was prescribed cyclical micronized progesterone. The treatment caused withdrawal bleedings for about six months and then her “menses” ceased, even though she was still on the medication. She was prescribed COC, which was effective in bringing back the withdrawal bleedings. She took the prescribed drugs for over two years.

On physical examination bilateral galactorrhea was found, along with hypopigmentation of the areola. Transvaginal ultrasound revealed: a hypoplastic corpus uteri (26 mm long, 16 mm thick and 20 mm wide), an endometrial strip linear, and small antral follicles in both ovaries (right volume 2.3 ml, left 2.6 ml).

Hormonal testing (see Table 1 for results) indicated severe hyperprolactinemia accompanied by hypogonadotropic hypogonadism. To assess pituitary function, the levels of IGF-1, ACTH and circadian rhythm of cortisol were determined. Additionally, a pituitary MRI scan, visual field test and DEXA scan were performed. The IGF-1, ACTH, and cortisol levels were within normal limits. The MRI scan showed a pituitary tumor, 13×18×17 mm, with characteristics typical of adenoma (see Fig. 1). The visual field was impaired, with partial bitemporal anopsia. Bone mineral density was normal.

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Table 1
The hormonal test results at the time of diagnosis.

Test	Result	Normal range
FSH [U/l]	2.35	1.70–7.70
LH [U/l]	0.11	2.40–12.60
PRL [ng/ml]	1639	5–25 ng/ml
E2 [pg/ml]	5.0	12.50–166.00
T [ng/ml]	0.52	0.06–0.82
DHEAS [μmol/l]	12.95	1.65–9.15
TSH [uIU/ml]	2.17	0.27–4.20

We initiated treatment with 0,5 mg cabergoline twice a week. After one month, the PRL concentrations had dropped to 112 ng/ml and, consequently, the dose was raised to 2 mg weekly. After another month, the PRL concentrations had decreased to 41 ng/ml. The polyethylene glycol (PEG) precipitation test showed that the majority of the PRL was in the form of macroprolactin (69.1%), so we decided not to increase the cabergoline dose. An ultrasound showed the thickness of the endometrium to be 6 mm and growing antral follicles. After 3 months of treatment, spontaneous menstrual bleeding occurred. We decided to continue the therapy with follow-up visits scheduled after 6 and 12 months. Fig. 1 presents the pituitary imaging before and after 12 months of treatment. The maximum diameter of the adenoma decreased 3 mm in the course of therapy and currently the patient is still taking medications and attending check-ups regularly.

3. Discussion

The patient presented with classical amenorrhea-galactorrhea syndrome in association with a pituitary macroprolactinoma. Unfortunately, it is also an example of a medical error, in that a previous diagnosis of menstrual disorders had to be abandoned. It is worth stressing that abnormal uterine bleeding should be always evaluated (though an exception may be made for otherwise asymptomatic girls one year after menarche) [4]. Initiating “treatment” with either progestins or COCs without performing any diagnostic testing is a common practice. In this case, in the past, hyperprolactinemia was not considered as a possible cause of abnormal uterine bleeding and therefore had not been detected. Moreover, hormonal treatment gave the patient and her family the false belief of being cured. It should be noted that a negative

progesterone withdrawal test (lack of menses after cyclical progestins) had been ignored, whereas it suggests the presence of profound hypoenstrogenism.

In the diagnosis of hyperprolactinemia, it is necessary to consider the possibility of a pituitary adenoma or another proliferative pathology of the hypothalamic-pituitary area. Adenomas are divided in terms of size into micro- (<10 mm) and macroadenomas (≥10 mm). Concentrations as high as in the described case (> 500 ng/ml) are considered to be diagnostic for macroadenoma and indicate the need for imaging (MRI is the preferred modality) and visual field assessment [1,2]. The impairment of other tropic cells should be taken into consideration, so measuring TSH, ACTH and gonadotrophin concentration is valuable. Considering the possibility of mixed PRL and growth hormone (GH) adenomas, the majority of authors recommend the simultaneous measurement of IGF-1 concentration [5]. If a patient has been exposed to profound and prolonged hypoenstrogenism, measurement of bone mineral density is indicated [1,2].

A clinician should be aware of diagnostic errors in cases of extreme hyperprolactinemia (PRL concentrations above 10,000 ng/ml). Very high PRL concentrations can saturate all of the immunoglobulin used in the assay and give the result of being abnormally low. This phenomenon is referred to as the “high dose hook effect”. In the case of a suggestive clinical picture (amenorrhea-galactorrhea) or pituitary adenoma in the MRI scan with normal or moderately elevated PRL concentration, this phenomenon should be taken into consideration [3]. Serum dilution before performing an immunoassay is the preferred management in such a case.

In the treatment of pituitary adenomas, dopaminergic agonists are the first-line treatment. Currently, the preferred drug is cabergoline, which is characterized by its greater efficiency and better tolerability compared with bromocriptine [2]. According to the available data, cabergoline allows restoration menstrual cycles in 78% of patients, stops galactorrhea in 86% and reduces the size of the adenoma by 62%. The starting dose is typically 0.5 mg in one or two divided doses per week. The effects of treatment are evaluated at intervals of about four weeks and the dose can be increased to 2 mg per week. MRI is recommended after 12 months in the case of microadenomas, and every three months in the case of macroadenomas, without improvement of PRL concentrations. For radical treatment, in cases resistant to pharmacotherapy and suspected malignant lesions, trans-sphenoidal adenoma resection is recommended [1–3].

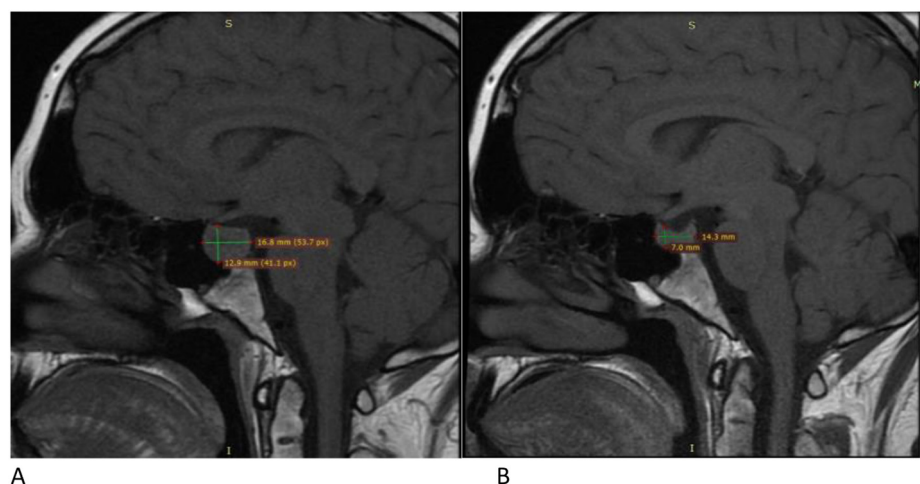


Fig. 1. MRI scan of the pituitary gland in the sagittal plane at the time of diagnosis (A) and after 12 months of cabergoline therapy (B).

Contributors

Both authors made a substantive contribution to the material submitted for publication.

Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

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Provenance and Peer Review

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