Chapter 2
When and How to Stop Cabergoline Treatment in Microprolactinomas

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Prolactinomas are the most frequent pituitary tumors with an estimated prevalence in the adult population of 100 per million population [1]. Their frequency varies with age and sex, occurring most frequently in women between 20 and 50 years of age; in the pediatric/adolescent age group, prolactinomas are rare, but represent about half of all pituitary adenomas [1].

Prolactin (PRL) excess causes gonadal and sexual dysfunction, while other symptoms related to the tumor expansion may occur in patients with large macroprolactinomas.

In the presence of clear-cut symptoms of hyperprolactinemia and after excluding pregnancy or the use of drugs known to induce increase of PRL levels [1], the diagnosis is made by serial PRL measurements and by magnetic resonance imaging (MRI) of the sella before and after contrast enhancement. Elevated (generally mildly) PRL levels in the absence of symptoms may be due to macroprolactinemia, while modestly elevated PRL levels in a patient with a large tumor may be expression of a pseudoprolactinoma (pituitary stalk section in a clinically nonfunctioning macroadenoma) [1]. However, in this latter case if PRL levels were measured by immunoradiometric assay (IRMA), the possibility of falsely low PRL levels by a hook effect should be verified by repeated PRL assay after dilution of blood samples [2].

To suppress excessive PRL secretion and its clinical consequences, such as infertility, sexual dysfunction, and osteoporosis, and to reduce the tumor mass, thereby relieving visual field defects, cranial nerve function and possibly hypopituitarism are the major objectives of treating patients with prolactinomas.

Dopaminergic agents, such as bromocriptine, lisuride, pergolide, and cabergoline, are considered the treatment of choice worldwide for either micro- or macroprolactinomas. Cabergoline has been shown more powerful and better tolerated than bromocriptine (3–7), and is tolerated very well by the large majority of patients.

In the past, treatment with dopaminergic drugs was considered to be necessarily continued lifelong due to the high recurrence rate at treatment withdrawal. More

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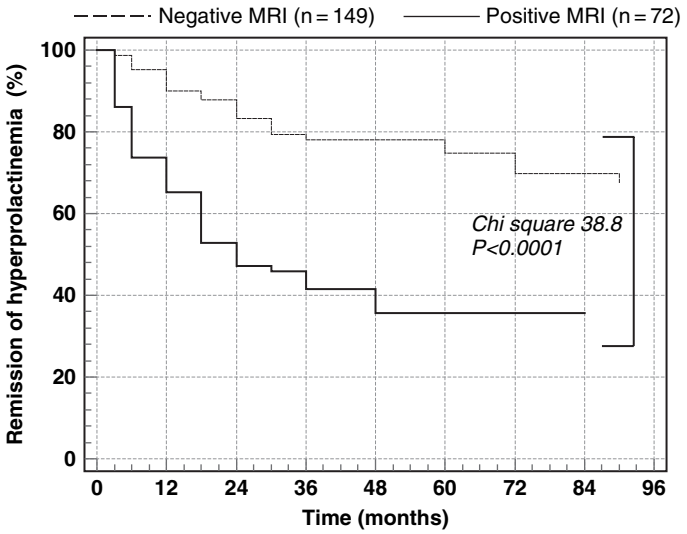

Fig. 2.1 Kaplan-Meier estimate of recurrence after 7 years of cabergoline treatment withdrawal. (Original data from ref. 1.)

recently, however, data have demonstrated a high prevalence of persistently normal PRL levels after withdrawal from cabergoline [8]. The remission rate after prolonged discontinuation of cabergoline treatment (median follow-up 72 to 90 months) was 68.4% in patients with nontumoral hyperprolactinemia, 51.8% in patients with microprolactinoma, and 52.5% in patients with macroprolactinoma [1]. The highest remission rates were found in the patients with nontumoral hyperprolactinemia or with disappeared microprolactinomas or macroprolactinomas during cabergoline therapy (Fig. 2.1). Importantly, at the last follow-up (48 to 90 months after cabergoline withdrawal) no recurrence of hyperprolactinemia was documented in the patients with no evident tumor on MRI later than 36 months.

The following case history of a 19-year-old woman with a microprolactinoma-induced amenorrhea describes the modality and outcome of cabergoline treatment withdrawal.

Case Presentation

M.M. came to our department for the first time in July 1997 at the age of 19 years because of amenorrhea lasting 5 months. She reported spontaneous menarche at the age of 13 years and oligomenorrhea since March 1996 associated with spontaneous bilateral galactorrhea. At our clinical examination, she had development of secondary sexual characteristics but axillary and pubic hair were faint while mammary glands were normally developed. At palpation, bilateral galactorrhea was found. Mean serum PRL levels at a diurnal profile were 98.5 μg/L (normal 5–25). At a

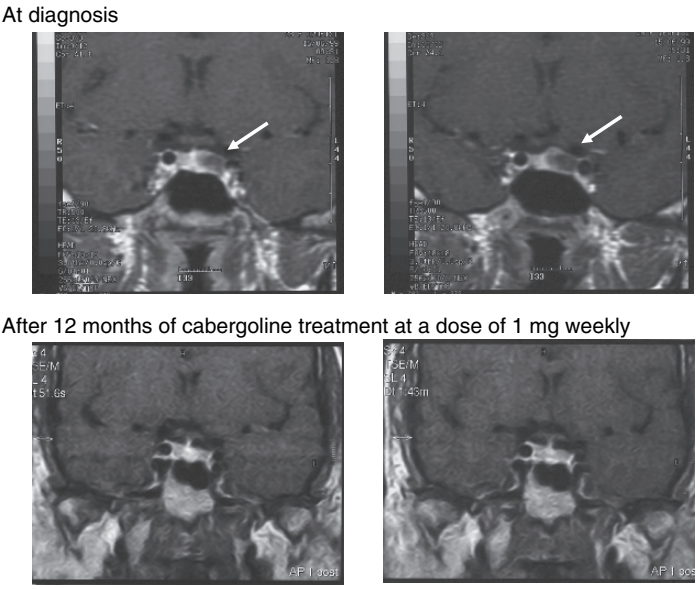

Fig. 2.2 Magnetic resonance imaging showing the 5-mm maximal diameter microprolactinoma located in the left portion of the gland (arrow) at diagnosis (top) and its disappearance after 12 months of cabergoline treatment (bottom)

sellar magnetic resonance imaging (MRI) with and without contrast enhancement, a pituitary microadenoma in the left paramedian portion was documented (Fig. 2.2). Thus, in accord with our routine clinical practice [8], in September 1997 the patient was started on cabergoline treatment at a dose of 0.5 mg twice weekly. Six months later, the mean serum PRL level was 3.6 μg/L, and we decided to continue cabergoline treatment at the same dosage.

At the 12-month follow-up after treatment, the mean serum PRL levels was 2.2 μg/L and the microadenoma was no longer visible on MRI (Fig. 2.2). In accord with our protocol [8], we decided to continue cabergoline treatment at a reduced dose to verify the possibility of subsequently withdrawing the patient from treatment. As shown in Figure 2.3, mean PRL levels remained stably in the normal range both at the dose of 0.5 mg weekly (3.8 μg/L) and 0.25 mg weekly (4.2 μg/L in a single dose). Since no microadenoma was documented on MRI performed in October 1999, treatment with cabergoline was stopped.

Cabergoline withdrawal was followed by a slight increase of PRL levels that remained in the normal range until the follow-up of January 2002. At this follow-up the mean serum PRL levels increased to 55 μg/L (Fig. 2.3). Since a PRL increase could have been caused by either recurrence of the microprolactinoma or pregnancy we performed a β–human chorionic gonadotropin (β-HCG) measurement that was 8500 mU/L (normal <50).

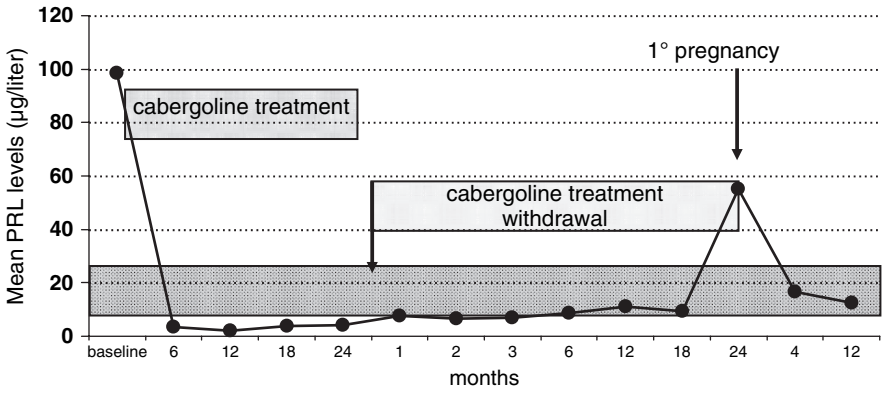

Fig. 2.3 Profile of mean prolactin (PRL) levels (diurnal profile of three to six blood samples) during the follow-up of patient M.M

On October 2, 2002, the patient delivered a healthy girl (length 51 cm, weight 3.1 kg). The patient was allowed to breast-feed her baby for 3 months. Subsequently, a reevaluation of mean PRL levels and sellar MRI were performed. Mean serum PRL levels was normal and a partial empty sella in the left paramedian portion of the gland was documented on MRI. Menses reappeared in February 2003. As shown in Figure 2.3, mean PRL levels remained normal to date. No change on MRI was found.

The patient had a second healthy pregnancy in April 2004. No recurrence of hyperprolactinemia or change on MRI were found at the follow-up performed in July 2006.

Lessons Learned

Cabergoline is considered the most effective drug for treating prolactinomas. Bromocriptine and pergolide are also very effective, but cabergoline fosters better patient compliance than bromocriptine and normalizes PRL levels even in patients resistant to bromocriptine (3–7). No comparative studies between cabergoline and pergolide are available. Note that asymptomatic patients with prolactinomas do not have an absolute requirement for treatment, since the major indications for therapy in patients with prolactinomas are to control tumor size and to reverse the effects of hyperprolactinemia [1].

The patient reported in this study had the classical amenorrhea-galactorrhea syndrome associated with a microprolactinoma, and there was no doubt that she needed to be treated. As per our routine clinical practice, the patient was informed of the benefits and risk of cabergoline and surgery, and she preferred to avoid surgery. Surgical removal of the microadenoma could also be considered a valid alternative to long-term pharmacotherapy with dopaminergic drugs, since the more modern

mini-invasive neurosurgical approach is very efficacious and results in the immediate relief of the clinical consequences of hyperprolactinemia [9, 10]. Recurrence of hyperprolactinemia is reported in approximately 20% at 10 years [1].

As already mentioned, recovery of gonadal function, control of tumor growth, and recovery from neurologic symptoms in patients with macroprolactinomas are generally obtained with primary dopamine agonist treatment [1]. In the past, cure of a prolactinoma has invariably been defined as the complete removal of tumor through surgical resection [11] due to the evidence that withdrawal from dopamine agonists (bromocriptine mainly) was followed by recurrent hyperprolactinemia in most cases [1]. In the first study reporting results of bromocriptine withdrawal, Johnston et al [12] reported recurrence of hyperprolactinemia in 94.6% of 37 patients even if PRL levels remained significantly lower than those prior to initiating therapy. Several other studies have confirmed the preliminary observation of Johnston et al (summarized in ref. 1). As a result, the principal shortcoming of dopamine agonist treatment has been its supposed lifelong requirement.

More recently, in an prospective, observational, and analytical study conducted in 200 patients with hyperprolactinemia undergoing cabergoline withdrawal, we reported a prevalence of recurrent hyperprolactinemia, independent of baseline tumor size, in less than 40% of the patients; thus, we anticipate greater long-term successful withdrawal with this drug [8]. In detail we found a Kaplan-Meier estimate of the recurrence rate of hyperprolactinemia after 5 years of cabergoline withdrawal of only 24% in patients with nontumoral hyperprolactinemia, and 32.6% in patients with micro- and 43.3% in those with macroprolactinomas without any MRI evidence of tumor regrowth. The highest remission rate was observed in patients with tumor disappearance during cabergoline treatment (Fig. 2.1).

Therefore, the case history reported in this study represents an exemplary case of patients with microprolactinoma with successful cabergoline treatment withdrawal.

Some other considerations should be addressed regarding this case. First, studies examining the natural history of untreated microprolactinomas have shown that significant growth of these tumors is uncommon [1]. Only nine (6%) of 139 women in six series of patients (with computed tomography [CT] evidence of microprolactinoma) observed without treatment for a period up to 8 years had evidence of microprolactinoma growth (13–18). Second, pregnancy [19, 20] and menopause [21] are conditions known to facilitate the remission of hyperprolactinemia, apart from previous surgery or radiotherapy and bromocriptine or cabergoline withdrawal.

In the patient reported in this study, pregnancy occurred after 2 years of successful cabergoline withdrawal. Delivery of a healthy girl was physiologic, and serum PRL levels normalized after the patient stopped breast-feeding as normally expected. In consideration of the long-term normalization of PRL levels after cabergoline withdrawal, it is unlikely that pregnancy was responsible for such a beneficial effect. In my opinion, it is more likely that pregnancy occurred because of the restoration of physiologic pituitary function than vice versa. A positive role of pregnancy in the persistence of normalization of PRL levels cannot be ruled out, however. It is, instead, uncommon that the simple observation of a microprolactinoma causing amenorrhea and galactorrhea is followed by remission of the disease, as

mentioned above. In such cases treatment (medical or surgical, according to the individual patient's preference) is indicated.

Conclusion

This case history of a young woman with a microprolactinoma-induced amenorrhea-galactorrhea syndrome demonstrates that 2 years of cabergoline treatment at a standard dose of 1 mg weekly in the first year and at a low dose of 0.25 to 0.5 mg weekly in the second year induced disappearance of the tumor together with normalization of PRL levels and restoration of normal pituitary-gonadal function. Withdrawal of cabergoline treatment was successful, but careful follow-up is required in all patients undergoing such an approach. In this case, successful withdrawal was accompanied by two successful pregnancies thereafter. Pregnancy-induced hyperprolactinemia could induce a misdiagnosis of recurrent hyperprolactinemia. Therefore, before cabergoline treatment is restarted, we suggest that β-HCG measurement be performed in all cases.

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Questions

1. Microprolactinomas are the most frequent pituitary tumors. True or false?
2. They invariably cause amenorrhea and galactorrhea in women. True or false?
3. The best treatment of microprolactinomas is

   A. Medical with dopamine agonists
   B. Surgical
   C. Both

4. Withdrawal from dopamine-agonist is invariably followed by recurrent hyperprolactinemia. True or false?