Hyperprolactinemia/Prolactinomas in the Postmenopausal Period: Challenges in Diagnosis and Management

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Keywords

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Abstract

Hyperprolactinemia is not a common finding in postmenopausal women. Prolactinomas detected after menopause are usually macroadenomas. Due to atypical clinical features they may remain unrecognized for a long period of time. Interestingly the growth potential of prolactinomas remains after menopause. Most tumors are invasive and present with high prolactin levels. They respond to medical treatment with dopamine agonists in terms of prolactin normalization, tumor shrinkage, and improvement in pituitary function. Treatment with dopamine agonists is usually long term. Reducing doses of cabergoline to the lowest that keeps prolactin levels normal prior to withdrawal is proposed to patients with macroprolactinomas who normalize prolactin after >5 years of treatment and who do not have cavernous sinus invasion. Cabergoline can achieve a high percentage of remission maintenance in the first years after withdrawal. However, the percentage of relapse-free patients 5 years after withdrawal is significantly lower. Besides recurrent hyper-

prolactinemia in a subgroup of macroprolactinomas after a long-interval tumor regrowth may be detected. Menopause cannot ensure remission of the tumor so long-term surveillance is suggested. In patients with microadenomas data on long-term remission rates (normalization of prolactin and disappearance of the tumor) after suspension of treatment with dopamine agonists are highly variable. The current strategy for microprolactinomas is not to treat hyperprolactinemia in menopause if it recurs after discontinuation of dopamine agonists. This is based on: (1) reports that elevated prolactin levels may normalize in some women after menopause, (2) the fact that the association between prolactin levels and breast cancer is inconsistent in postmenopausal women, (3) the lack of clinical evidence that normalization of prolactin levels in postmenopausal women improves bone mineral density or reduces the risk of fracture, and (4) the fact that, concerning the metabolic syndrome, no data are available on metabolic parameters after suspension of treatment with dopamine agonists. For a change in strategy, i.e., for the potential benefits from treatment of hyperprolactinemia in the postmenopausal period with dopamine agonists concerning weight loss, improved insulin sensitivity, decreased fracture risk, and improved sexuality, more evidence is needed.

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Introduction

The published literature on (1) prolactinomas diagnosed in postmenopausal women as well as on (2) the impact of menopause on outcomes in prolactinomas after dopamine agonist withdrawal is very limited [1–4]. Most women diagnosed with prolactinoma after menopause had no specific complaints or had symptoms related to the tumor mass effect. The clinical features differ from prolactinomas diagnosed in the premenopausal period, which usually present with amenorrhoea, infertility, and galactorrhoea. The majority of prolactinomas diagnosed in postmenopausal women are macroadenomas unlike in premenopausal women in whom microadenomas are more commonly reported. In males macroprolactinomas are diagnosed at an older age than in women with microprolactinomas [5]. The gender-related age difference at diagnosis of giant prolactinomas in women is opposite to that in men, i.e., women are older at diagnosis [6]. In many instances, the long delay in diagnosing prolactinomas in women may be due to the frequent use of oral contraception (regular cycles despite hyperprolactinemia) or intrauterine levonorgestrel-releasing devices, so that the clinicians cannot rely anymore on the gonadal effects of hyperprolactinemia [7].

Diagnostic Challenges

Prolactinomas diagnosed in women after menopause are usually large and invasive and they are diagnosed because of symptoms of a pituitary mass. Galactorrhoea is an inconstant finding in women with macroprolactinomas (37.5%) [5]. Data regarding galactorrhoea may be underestimated because it may not have been recorded. In a recent study, galactorrhoea was present in 8 out of 24 patients with giant prolactinomas and it was never recorded after the age of 50 years [6]. Giant prolactinomas are rare in women and they are usually diagnosed at a later age in women with a long-standing history of amenorrhoea. These macroadenomas may represent the natural course of an untreated prolactinoma. The long delay before diagnosis may be related to personal and social factors. In a recent study in a total female population of 34 patients with giant prolactinomas, a later-onset group consisted of 24 patients with a median age at onset of 44 years. The delay in the diagnosis of giant prolactinomas in women ranged from 2 to more than 30 years [6]. The most common symptoms of macroprolac-

tinomas in postmenopausal women are visual field disturbances and headache, but also other atypical presentations such as impaired hearing, hemiparesis, dementia, and new-onset epilepsy have been reported [7]. In a study, 6 out of 29 patients with macroprolactinomas with suprasellar extension invading/compressing the surrounding brain structures had a history of seizures at the time of diagnosis [8]. Two out of 6 patients were females aged 52 and 61 years. The presenting symptoms compatible with temporal epilepsy in these 2 females were: oral automatism, loss of awareness, aphasia, disorientation, and amnesia. The mechanisms underlying tumor-associated seizures remain to be determined. Following treatment with dopamine agonists, which enhanced dopamine levels, improved seizure control was achieved [9].

Postmenopausal woman with macroprolactinomas may also present with a sudden onset of severe headache, nausea, and malaise. Pituitary MRI demonstrates a heterogeneous mass with peripheral enhancement after gadolinium injection. The diagnosis of pituitary apoplexy usually occurs in a previously unknown pituitary adenoma. In a recent study acute pituitary apoplexy diagnosed at presentation or during follow-up was found in 18% of 17 patients diagnosed with prolactinoma in the postmenopausal period at a median age of 63 years [3]. Magnetic resonance imaging studies have confirmed that prolactinomas are frequently hemorrhagic in women [9]. Most are asymptomatic (subclinical apoplexy) and resolve spontaneously [10, 11].

As for hormonal evaluation, serum prolactin levels usually parallel tumor size. Nowadays in very rare instances there may be a discordance between tumor size and prolactin levels. The patient may have a giant skull base tumor with falsely low serum prolactin concentrations. Accurate prolactin values should be obtained after serum sample dilution in order to overcome the “hook effect” due to very high antigen levels [12, 13]. Thus, despite the accuracy and specificity of modern assays, the “hook effect” can still occur.

Therapeutic Challenges of Hyperprolactinemia/ Prolactinomas in Postmenopausal Women

Cabergoline is the first-line therapy for macroprolactinomas diagnosed at menopause and in most patients it is highly effective in terms of both hormonal and tumoral responses. In most patients with macroprolactinomas symptoms are quickly relieved with dopamine

agonists, serum prolactin levels normalize, and a reduction in tumor size occurs. Treatment with dopamine agonists is also associated with better outcomes in terms of pituitary function [5]. Cabergoline can achieve remission maintenance after cessation of a 5-year course of therapy in patients with macroprolactinomas [14]. Factors related to remission after withdrawal of cabergoline in patients with macroprolactinomas receiving treatment for >5 years are: absence of cavernous sinus invasion, lower serum prolactin levels before therapy, and low nadir serum prolactin on cabergoline therapy prior to withdrawal [13]. In a recent French study on management of macroprolactinomas the dose of dopamine agonist was usually reduced to the minimum required to maintain normal prolactin levels and achieve tumor volume control. The duration of cabergoline therapy was longer in resistant patients. Tapering the cabergoline dose was almost always possible [15].

The concept that menopause facilitates the remission of hyperprolactinemia in women with prolactinoma may be seen in about 50% of patients after dopamine agonist withdrawal [4]. Long-term remission (>10 years) is seen in postmenopausal patients with macroprolactinoma who did not have cavernous sinus invasion. Tumors sensitive to dopamine agonists are more likely to show persistent remission of hyperprolactinemia after treatment withdrawal [16]. Not all tumors are equally sensitive to dopamine agonists (i.e., some are less responsive). The most commonly used definition of dopamine agonist resistance includes failure to normalize prolactin and/or failure to achieve at least 50% shrinkage of the tumor with maximal conventional doses of cabergoline (2 mg/week). In a French retrospective study of a large cohort of patients with macroprolactinomas, 19.6% of the patients received doses of cabergoline >2 mg/week [15]. The dose of cabergoline was incremented in order to normalize prolactin up to 8 mg/week. Ten percent of the patients still had a partial resistance to cabergoline (did not normalize prolactin). Even higher doses of cabergoline (11 mg/week) have been suggested in order to overcome resistance to treatment [17]. In the mentioned French study, patients with a partial resistance to cabergoline in whom cabergoline withdrawal was successful did not show renewed tumor growth [15]. However, despite this appealing concept there is a subset of female patients with prolactinomas who will show growth potential with time in menopause. Regrowth of residual adenoma may be detected despite low prolactin levels while on cabergoline therapy. Age does not ensure tumor stability on therapy.

Studies have reported that tumor response in macroprolactinomas is not correlated with age, gender, baseline prolactin levels, or tumor size [7]. In a recent study on the long-term outcomes of discontinuation of dopamine agonist treatment in women with prolactinoma after menopause, residual adenoma regrowth was detected in 7% (2 out of 22) of the patients [3].

The role of surgery in macroprolactinomas is difficult to establish. The indications for surgery are CSF rhinorrhoea, pituitary apoplexy, and tumor progression or regrowth despite medical treatment [7]. Following surgery the pathology report is of particular interest to define the precise type of adenoma. Radiotherapy may be used postoperatively in proliferative tumors. Few patients who received radiation therapy after dopamine agonist withdrawal had normal prolactin levels and disappearance of the tumor. This occurs 5 and 10 years after radiation therapy. Radiotherapy is associated with hypopituitarism.

To Treat or Not to Treat Hyperprolactinemia after Active Withdrawal of Dopamine Agonist Therapy in Postmenopausal Women Who Have Microprolactinomas?

In a meta-analysis, recurrence of hyperprolactinemia in patients with microprolactinomas after suspension of treatment with dopamine agonists was observed in 21% of the patients [18]. Recommendations from the guidelines are that, after >2 years of successful treatment (normal circulating prolactin and disappearance of the tumor) as well as in menopause, dopamine agonist therapy could be tapered and discontinued [19]. Women who go through menopause have a chance of normalizing prolactin levels. In recent study, the risk of recurrence of hyperprolactinemia was lower in the postmenopausal period [1, 2, 4].

Prolactin Levels and Bone

Patients with prolactin-secreting tumors have decreased bone mineral and the bone loss is associated with an increase in bone resorption due to prolactin-induced hypogonadism. Normalization of prolactin and restoration of gonadal function increase bone density but this is not associated with normalization of bone mass. Some studies have shown that, despite the low bone density, hyperprolactinemic subjects do not dem-

onstrate increased fractures [20]. On the other hand, other studies have reported a higher prevalence of vertebral fractures in postmenopausal women with untreated prolactinomas versus patients treated with cabergoline [21]. Thus, beside the effects of hyperprolactinemia on gonadal function, the effects on bone can be independent of gonadal function [22]. Prolactin excess per se may contribute to skeletal fragility [23]. However, there are no prospective studies showing that normalization of prolactin levels in postmenopausal women improve BMD or reduce the fracture risk [24].

Prolactin Levels and Tumorigenesis

Epidemiological studies on the association of hyperprolactinemia and cancer risk in humans have yielded inconsistent results from showing a small but increased cancer risk to no risk at all [25–27]. No association has been found between the development of breast cancer in premenopausal women and hyperprolactinemia, while inconsistent findings have been observed in postmenopausal women [24]. The reason for the inconsistent results in different studies is that large samples are required with a long follow-up time. Furthermore, these associations may not be causative. The actual contribution of prolactin to breast cancer is still lacking. The concerns regarding hyperprolactinemia and cancer risk have been attributed to the demonstration of the role of prolactin receptor in tumorigenesis, the involvement of autocrine/paracrine prolactin production in disease progression, and the availability of prolactin-receptor blockers. The extrapolation of these findings from experimental models to humans is not straightforward [28].

Morbidity in Patients with Hyperprolactinemia

Hyperprolactinemia has been associated with adverse health outcomes in some studies. Although some initial studies suggested that prolactin might promote platelet aggregation, patients with prolactinomas do not appear to have a higher risk of thrombosis [29, 30]. Also recent studies have not shown that increased prolactin levels are associated with cardiovascular disease nor diabetes mellitus [27]. There is no dose-response relationship between the extent of serum prolactin elevation and the risk of adverse outcomes, indicating that the association is not direct. The role of prolactin in autoim-

mune disease is unclear, with no translation into the clinic yet. Hyperprolactinemia has been associated with weight gain and obesity and linked to insulin resistance [31, 32]. It has been shown that dopamine agonist therapy can improve metabolic syndrome in patients with a prolactinoma and lower glucose levels in patients with diabetes [33]. However, no data are available for the effect of hyperprolactinemia on metabolic parameters in women in the postmenopausal period and whether they should be considered as candidates for dopamine agonist therapy [34].

Prolactin and Female Sexual Dysfunction in Menopause

Women in menopause, because of a complex interplay of individual factors, are vulnerable to sexual dysfunction which affects their well-being. The impact of age and menopausal estrogen loss on sexuality has been reviewed in the literature [35]. In clinical practice, changes in sexual desire are rarely a matter for which physicians are consulted, despite their high prevalence [36]. Hormones are only one component of the many factors that contribute to normal sexual function in women [37]. Data on the impact of common endocrinopathies on female sexual function are limited [38]. Further research is required to determine the contribution of hyperprolactinemia to female sexual function in postmenopausal women and whether medical treatment with dopamine agonists would lessen sexual dysfunction.

Conclusion

Prolactinomas in women in menopause are rare, they are macroadenomas usually presenting with atypical features, thus posing a diagnostic challenge. Medical therapy with dopamine agonists is highly effective in terms of normalization of prolactin levels and a significant reduction of the tumor size. Menopause may facilitate normalization of prolactin, and a lower recurrence of hyperprolactinemia after withdrawal of treatment with dopamine agonists is reported. However, menopause does not ensure remission in tumor growth, particularly in invasive macroprolactinomas. The current concept is that patients with microprolactinomas should actively be withdrawn from dopamine agonist therapy in menopause regardless of the possibility of re-

currence of hyperprolactinemia. A major limitation of this strategy is that the published literature on outcomes in prolactinomas after dopamine agonist treatment withdrawal is scarce.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Discosure Statement

The authors have no conflicts of interests to declare.

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Author Contributions

S.P., M.M.S., and V.P. wrote the minireview.

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