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DOI:
10.1111/cen.13399

CLINICAL ENDOCRINOLOGY

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Journal:	*Clinical Endocrinology*
Manuscript ID	CEN-2017-000379.R1
Manuscript Type:	1 Original Article - UK, Europe
Date Submitted by the Author:	06-Jun-2017
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Key Words:	Prolactinoma < Conditions: < Pituitary, Cabergoline < Investigations & Rx: < Pituitary, Dopamine agonists < Investigations & Rx: < Pituitary,

	menopause

Prolactinomas diagnosed in the postmenopausal period: clinical phenotype and outcomes

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Short title: Prolactinomas detected after menopause

Keywords: Prolactinoma, menopause, dopamine agonists

Conflict of interest: None

Abstract

Objective: Most prolactinomas in females are diagnosed during the reproductive age and the majority are microadenomas. Prolactinomas detected in the postmenopausal period are less common with limited published data on their presentation and prognosis. Our objective was to assess the presenting clinical, biochemical and imaging findings, as well as the outcomes of women diagnosed with a prolactinoma in the postmenopausal period.

Design and Methods: We undertook a retrospective cohort study of women diagnosed with prolactinoma after menopause and followed-up in a large UK pituitary center. Information on presentation, management and outcomes were collected.

Results: Seventeen women with a median age at diagnosis of 63 years (range 52-78) were identified. Headaches and/or visual deterioration were the most commonly reported complaints at detection of the adenoma (47%). Acute pituitary apoplexy was diagnosed at presentation or during follow-up in 18% of the cases. The median serum prolactin was 12364 mU/L (range 2533-238479). Macroprolactinomas comprised 94% of the tumours, and 88% of them had supra/parasellar extension. All patients with macroprolactinoma were offered dopamine agonist and normal prolactin was achieved in 94% of them (median follow-up 91.5 months). Adenoma shrinkage was observed in all women. Improvement or resolution of visual disturbances documented at presentation was observed in 86% of cases.

Conclusions: The clinical phenotype of prolactinomas diagnosed in the postmenopausal period is characterized by dominance of macroadenomas, with frequent supra/parasellar extension and a relative high rate of acute pituitary apoplexy. In this group of patients, the response of the macroadenomas to dopamine agonists is good.

Introduction

Prolactinomas have a prevalence of 35-44/100,000 population and are the most common pituitary adenomas diagnosed in women (1-3). Most prolactinomas in females are diagnosed during the years of reproductive age (median 30.5-32 years), and the majority are microadenomas (1,3) that show a high response rate to cabergoline (93%) (4). In contrast, prolactinomas in males are diagnosed at an older age (median 41.5-47.5 years) and are mostly macroadenomas (1,3).

Experimental data in rats have shown that ooophorectomy has a dramatic effect on lactotroph cells, with a decrease in their size and number, as well as a reduction in the intracellular abundance of PRL-secretory granules; all these effects are reversed by estradiol (5). Interestingly, *in vivo* estrogen administration induces lactotroph tumours in rats (6) and selective antiestrogen treatment inhibits lactotroph tumour growth in rats harboring subcutaneous implanted PRL-secreting pituitary tumours (7). Although a number of studies in humans do not support an association between use of oral contraceptives or estrogen replacement therapy and prolactinoma formation or growth in women (at least in microadenomas), these adenomas may enlarge during pregnancy, and cases of prolactinomas occurring after long-term estrogen therapy in male-female transsexuals have been reported (8,9). Menopause, a physiological state of hypoestrogenism, can have a beneficial effect on the natural history of hyperprolactinemia. A small number of studies have shown that long-term reduction or normalization of PRL in women with microprolactinoma after the cessation of their menses can occur (10,11), and, therefore, stopping treatment with dopamine agonist may be a justified approach.

Females diagnosed with a prolactinoma in the postmenopausal period represent a less common and possibly under-recognized group, as the compromised ovarian function alters the presenting clinical manifestations and the changes in the estrogen status may have an impact on the natural history of the tumour. In fact, epidemiological studies report standardized incidence rates of around 1/100,000 for prolactinomas diagnosed in females aged above 50 years (2,3). As a result of this, data on their clinical phenotype, natural history and outcomes are extremely limited, with only a single report published to date (12); this involved a case series of 14 patients from three different Endocrine outpatient clinics in three academic centers from Israel, USA and Brazil. Therefore, and taking into

account the reported impact of menopause on PRL secretion, studies providing further insight on this specific group of patients would be of value in clinical practice.

The aim of our study was to assess the clinical, biochemical and imaging findings at presentation and during follow-up, as well as the outcomes of women diagnosed with a prolactinoma during the post-menopausal period and managed in a single pituitary center in the UK.

Patients and Methods

Patients

All females with a prolactinoma diagnosed in the postmenopausal period (mean age of menopause in the UK 51 years) and reviewed in the Department of Endocrinology, Queen Elizabeth Hospital Birmingham, UK between 1996 and 2016 were studied. These were identified through searches by the University Hospitals Birmingham IT Services in the electronic patient record, as well as through searching the Departmental database. The diagnosis of prolactinoma was based on the detection of hyperprolactinemia (after excluding the presence of macroprolactin and secondary causes explaining the PRL levels) combined or not with the identification of an adenoma on pituitary imaging; it was further supported by shrinkage of the tumour in cases in which dopamine agonist therapy was offered or by the presence of positive PRL immunostaining in tumours surgically resected. Clinical, biochemical, imaging findings and medications at presentation and follow-up, as well as information on the management and outcomes of the patients were collected.

In cases in which dopamine agonist therapy was offered, the dose was gradually titrated until achievement of normal PRL or until maximum tolerated dose was achieved. Pituitary imaging was performed within 6 months after starting treatment and at clinically indicated intervals thereafter. The assessment of visual fields was performed by Goldman perimetry.

The study was completely retrospective in nature and involved no intervention beyond routine patient care. It was registered with and approved as an audit by the University Hospitals Birmingham NHS Foundation Trust.

Prolactin assay

The serum PRL was measured between 1996 and 2000 by a Corning ACS immunometric assay, between 2000 and 2006 by a Bayer Advia Centaur immunometric assay (reference range for both assays: males 40-360 mIU/L; females 60-620 mIU/L), and between 2006-present by an E170 Roche

Diagnostics immunometric assay (reference range: males 85-325 mIU/L; females 100-500 mIU/L). All assays were standardised to IRP 84/500.

Statistics

Percentages were calculated for categorical data and medians with ranges for continuous variables. Correlation between age and PRL levels at diagnosis were performed by the Pearson's correlation method. The level of significance was set at $p<0.05$. Statistical analyses were performed by IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

Results

Seventeen women diagnosed with a prolactinoma at a median age of 63 years (range 52-78) were identified. No patient was on estrogen replacement therapy at the time of detection of the tumour. The presenting clinical, biochemical and imaging manifestations are shown in Table 1.

Headaches and/or visual deterioration were the most commonly reported complaints at detection of the adenoma [8/17 (47%)]. Two patients presented with pituitary apoplexy [2/17 (12%)]; in one of them, serum PRL was normal at the time of apoplexy, which was managed by transsphenoidal surgery (pathology consistent with a necrotic pituitary adenoma); seven years later, PRL was found at 12364 mU/L, leading to the final diagnosis of prolactinoma. The second case of apoplexy was managed conservatively. Two prolactinomas were detected incidentally (12%).

In terms of menstrual history, five women had a history of amenorrhea for which they had no investigations during the reproductive age; their prolactinoma was diagnosed at the ages of 52, 60, 63, 65 and 66 years; two had hysterectomy at the age of 29 and 34 and were diagnosed when 70 and 58 years, respectively; in all other cases, early menopause was not reported.

All patients except one (who had a 5 mm adenoma) had macroprolactinoma (16/17, 94%), with supra/parasellar extension in 15/17 of them (88%). Visual field defects attributed to pressure on the optic pathways by the adenoma were identified in 7/17 (41%) patients.

The serum PRL of the single microprolactinoma patient was 2533 mU/L; in those with macroprolactinoma, the median value was 18553 mU/L (range 4153-238479). There was no significant correlation between age and PRL levels at diagnosis. In all cases, IGF-I values were not consistent with GH hypersecretion. At diagnosis, two patients were put on glucocorticoid replacement for ACTH deficiency and four were on Levothyroxine.

The management and the outcomes of the patients are shown in Table 2. The patient with the microprolactinoma was not treated with dopamine agonist and her PRL rose from 2533 to 3227 mU/L during a follow-up period of 51 months; pituitary MRI 26 months after the original imaging did not identify an adenoma. During follow-up, she was on opiates for pain relief, which may have

contributed to persistence of the hyperprolactinemia. All patients with macroprolactinoma were offered dopamine agonist therapy (cabergoline n=13, bromocriptine n=2, quinagolide n=1). The median duration of their follow-up, determined by the date of starting dopamine agonist until last serum prolactin measurement, was 91.5 months (range 5-222). Normal PRL was achieved in 15/16 (94%) patients, and this did not prompt menstrual bleeds in any of them [their gonadotropins remained suppressed (n=10) or reached the menopausal levels (n=6)]. Adenoma shrinkage was observed in all women (ranging from 25% reduction in maximum diameter up to complete adenoma resolution on latest imaging). All but one patients (6/7, 86%) had improvement or resolution of the visual disturbances documented at presentation. One patient presented with apoplexy (sudden onset headache and right visual loss) eight months after starting cabergoline; she was surgically managed (pathology: adenoma with immunostaining positive for PRL and focal apoplexy) and restarted cabergoline due to residual adenoma. Treatment was stopped in two patients [one on cabergoline following her choice with PRL showing slight increase 6 months later (561 mU/L, 100-500), and one on bromocriptine with PRL increasing due to commencing olanzapine, but with imaging 10 months later not showing adenoma enlargement].

Discussion

This is the largest study to date assessing the clinical phenotype and outcomes of consecutive cases of prolactinomas diagnosed at the postmenopausal period. While in premenopausal women microprolactinomas dominate, we found that 94% of the tumours newly diagnosed in our postmenopausal patients were macroadenomas, and these caused headaches and/or visual deterioration in almost half of the cases. Despite the size of the tumours (macroadenomas with supra/parasellar extension in 88% of them), the response to dopamine agonists was very good, both in terms of achieving normal PRL and adenoma shrinkage. Interestingly, apoplexy was seen in 18% of the cases at diagnosis or during follow-up.

The absence of menstrual irregularities in postmenopausal women harboring a prolactinoma results in a different clinical phenotype leading to diagnosis of the tumour. Thus, the sequelae of hyperprolactinemia are not evident (apart from the rare cases of galactorrhea) and the consequences of a pituitary mass lesion, headaches and/or visual disturbances, are the most common presenting manifestations (47% in our series). Interestingly, two cases (12%) were diagnosed incidentally and involved adenomas with PRL of 9046 and 11401 mU/L, respectively, and minimal or no suprasellar extension. It is also of note that five women had a history of long-standing amenorrhea for which no investigations had been carried out during reproductive age; their macroadenoma was diagnosed between the ages of 52-66 years. Although these may not relate with the prolactinoma, the long-standing presence of the tumour cannot be excluded, reflecting the natural history of untreated prolactinoma.

Interestingly, pituitary apoplexy was the first presentation in two of our patients. Although extracted from a small number of cases, this percentage is remarkable compared with the reported apoplexy rate of 0.81% in a series of 368 prolactinomas treated in a single center during a period of 11 years (upper interquartile range for age at diagnosis in females and males: 37 and 54.5 years, respectively) (13). In the same paper, macroadenoma and female gender were strongly predictive of the presence of pituitary hemorrhage (not necessarily associated with clinical picture of apoplexy) on MRI (13). A rapidly expanding adenoma that outstrips its blood supply and results in ischemia/hemorrhagic

infarction, as well as compression of the pituitary vessels at the diaphragmatic notch have been proposed as potential mechanisms (13,14). In our study, pituitary apoplexy was diagnosed in a third patient 8 months after starting cabergoline. This necessitated transsphenoidal surgery due to visual deterioration; cabergoline was subsequently restarted with no further apoplectic event as of latest assessment. Cases of patients with pituitary apoplexy whilst on dopamine agonist have been previously described (15); a potential causal link and the mechanism of this remain to be clarified. Overall, the rate of apoplexy in our patient group was 18%. It is of note that in epidemiological studies looking at the prevalence of prolactinomas, the overall rates of apoplexy range between 0% and 2.7% (1-3). Whether post-menopausal women with prolactinoma are predisposed to pituitary apoplexy, or whether our finding is a mere coincidence remains to be elucidated.

It has been previously suggested that PRL levels usually reflect tumour size (16). We attempted to clarify if PRL values also correlate with age at diagnosis in the group of postmenopausal women but our analysis did not support this.

We found that 94% of the prolactinomas were macroadenomas with often invasive behaviour; supra/parasellar extension was detected in 88% of the tumours. This is in contrast to the imaging features seen in premenopausal females, where the majority are microadenomas: 70% in a series of 51 females aged at diagnosis 28±1 years (16) and 85% in a series of 325 females with median age at diagnosis of 31 years (interquartile range 25-37) (13). However, the true prevalence of microprolactinomas in postmenopausal women is difficult to ascertain, as the manifestations of hyperprolactinemia are usually not clinically relevant and possibly a number of postmenopausal females harboring this type of tumour escape diagnosis. In fact, in a meta-analysis, the prevalence of pituitary adenoma from autopsy studies was 14.4% and, when immunohistochemical staining took place, PRL positive cells were identified in 25-41% of the specimens, indicating that a significant number of prolactinomas may not be diagnosed during the life-span (17). Published literature suggests that in males, prolactinomas are diagnosed at an older age, and, as in the postmenopausal women, there is a predominance of large and often invasive tumours (63-89% being macroadenomas) (2,3,16,18,19). Although not widely accepted (20), this may be attributed to a true gender difference

in adenoma behaviour with higher proliferative activity in males (16). It should be noted, however, that bias related with the selection and study of surgically-only managed tumours may influence the validity of these reports.

In our series, we did not confirm aggressive adenoma behaviour in postmenopausal women; treatment with dopamine agonists led to normal PRL and to tumour shrinkage in 94% and 100% of the macroprolactinomas, respectively. Previous studies including both males and females of all ages with macroprolactinoma showed that cabergoline led to normoprolactinemia in 61-89% and tumour shrinkage (using various criteria) in 55-73% of cases (4, 21-23). Furthermore, in a report including females with giant prolactinoma (defined as a tumour larger than 4 cm and PRL above 1000 mcg/l), 7/18 (39%) of the patients were resistant to weekly doses of cabergoline ranging from 3 to 7 mg (24). Notably, it has been suggested that gender may not have an independent influence on success rates (4, 25), but this view has not been confirmed by others (26) who propose that male gender is independently associated with resistance to cabergoline. Reports focusing on macroprolactinomas in men treated with cabergoline have shown PRL normalization rates between 75.6 and 90% (19,27).

The published literature on prolactinomas detected after menopause is limited with only one report published of a case series from three different Endocrine outpatient clinics in three academic centers from Israel, USA and Brazil (12). They authors identified 14 women who were diagnosed with a prolactinoma after menopause; 5/14 (36%) had no specific complaints when diagnosed, 6/14 (43%) had reported headaches and/or visual disturbances, 2/14 (14%) had galactorrhea and one (7%) had diplopia. Similar to our study, 93% had macroadenomas; suprasellar extension was seen in 57% and visual field defects were detected in 43%. Median PRL was 827 ng/ml (17532 mU/L) (range 85-6732 ng/ml). Cabergoline was offered to 12 patients who were followed-up for a median period of 66 months; in agreement with our results, optimal response was seen with PRL normalization in 10 (83%) and reduction in adenoma size (of various degrees) in 11 (92%) of cases.

A potential limitation of our study is the lack of data on adenoma behaviour after stopping the dopamine agonist treatment in this age group. Collaborative studies would be required to reliably address this question, and also to clarify the natural history of prolactinomas diagnosed after

menopause and not treated with dopamine agonists (due to lack of pressure effects). The advantage of our study is the inclusion of a large number of cases, which were also non-selected, consecutive and with detailed clinical characterization, managed with a similar approach in a single center.

In conclusion, the clinical phenotype of prolactinomas detected in the postmenopausal period differs from that of premenopausal women. Macroadenomas with often invasive behaviour dominate and the mass effect leads to most of the signs and symptoms that prompt investigations and diagnosis. The rate of pituitary apoplexy was high in our series, and this, although requiring further confirmation, needs to be kept in mind. Nonetheless, it is very reassuring to confirm that medical treatment is highly effective in this group of patients.

Funding: This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Table 1. Presenting clinical, biochemical and imaging manifestations of the women with prolactinoma diagnosed in the postmenopausal period

No	Age at diagnosis	Clinical Manifestations	PRL at diagnosis (mU/L) (reference range)	Macro/ Micro (max dimeter – cm)	Extensions of prolactinoma
1	78	Nausea, lethargy, tiredness, unsteadiness, cold intolerance (manifestations of hypopituitarism)	22957 (100-500)	Macro (3.2)	Sphenoid sinus, suprasellar displacing chiasm, distortion of 3rd ventricle
2	70	During investigations for increased sweating and suppressed FSH Note: hysterectomy aged 34 (no galactorrhea reported at any time between hysterectomy and diagnosis of prolactinoma)	2533 (100-500)	Micro (0.5)	Left-sided
3	70	Pituitary apoplexy with left 3rd cranial nerve palsy Note: history of diabetes mellitus and hypertension	At time of apoplexy 155 At time of prolactinoma diagnosis 12364 (100-500)	Macro	At time of apoplexy: sphenoid sinus, left cavernous sinus invasion At time of prolactinoma diagnosis: left sided mass projecting into the sphenoid sinus
4	60	Tiredness, galactorrhea Note: history of amenorrhea for which the patient had been put on estrogen replacement therapy until age of 50	35105 (100-500)	Macro (2.8)	Sphenoid and cavernous sinuses, minor suprasellar extension
5	58	Obstruction of left nostril, nasal drip and nosebleeds - CT performed to check for nasal polyp and biopsy of lesion confirmed prolactinoma	39365 (100-500)	Macro (3.4)	Fills sphenoid sinus, destruction of right petrous apex, right cavernous sinus invasion
6	58	Headaches Note: hysterectomy aged 29 (no galactorrhea reported at any time between hysterectomy and diagnosis of prolactinoma)	4400* (60-540)	Macro (1.6)	Left cavernous sinus
7	60	Visual deterioration	32898 (100-500)	Macro (3.4)	Suprasellar, cavernous and sphenoid sinuses
8	65	Amenorrhea since age 21 - finally investigated at age 65	41680 (60-620)	Macro (3.8)	Cavernous sinuses

9	55	Visual deterioration Note: menstrual irregularities since her 40s	238479 (60-620)	Macro (4.2)	Fills sphenoid sinus, extends down into the base of the pterygoid plate, forward into the region of the posterior ethmoid, laterally to cavernous sinuses, superiorly into the suprasellar system displacing optic nerves and chiasm, supero-anteriorly up to the region of the cribiform plate
10	52	Headaches, visual deterioration	12040 (60-620)	Macro (4.1)	Cavernous sinuses, encasing carotids, posteriorly closely related to anterior aspect of basilar artery, extension into middle cranial fossa, posteriorly into adjacent part of interpeduncular system, into the suprasellar area involving optic chiasm and floor of third ventricle
11	67	Visual deterioration	>9000* (65-615)	Macro (2.1)	Suprasellar, cavernous and sphenoid sinuses
12	63	Incidentally after investigations for increased sweating and detection of low gonadotropins Note: periods stopped at age of 43	9046 (60-620)	Macro (1.5)	Left cavernous sinus, mild suprasellar extension
13	66	Visual deterioration Note: periods stopped in her 30s	5166 (60-620)	Macro (4.4)	Extensive destruction of the clivus, spreads up onto the planum sphenoidale, extends into both sphenoid sinuses and out to the left cerebellar pontine angle, diaphragm of the pituitary is concave but tumour spreads out on the right into the mesial aspect of the temporal lobe
14	58	Incidentally found after investigation for trigeminal neuralgia	11401 (100-500)	Macro (1.3)	Intrasellar
15	72	Visual deterioration	46003 (60-620)	Macro (4.5)	Cavernous sinuses, widely splaying the cavernous carotid vessels, suprasellar, impinges and indents on the third ventricle superiorly, hypothalamus and mammillary bodies, effacement of the prepontine cistern and mild indentation of the anterior pons, erosion of the dorsum sellae and posterior clinoid, mild obstructive hydrocephalus
16	62	Pituitary apoplexy with sudden onset of headache, nausea, bitemporal hemianopia	4153 (100-500)	Macro	Sphenoid sinus and suprasellar

17	52	Visual deterioration Note: periods stopped at age of 35	18553 (60-620)	Macro (2.1)	Sphenoid sinus and suprasellar

*PRL checked in a different lab.

Table 2. Management and outcomes of women with prolactinoma diagnosed in the postmenopausal period

No	Dopamine agonist	Maximum dose of dopamine agonist	Last dose of dopamine agonist	Normalization of PRL	Treatment duration (months)	Adenoma shrinkage >25% in max diameter
1	Cabergoline	0.5 mg/week	0.5 mg/week	Yes	58	Yes
2	None	-	-	-	-	-
3	Cabergoline	0.5 mg/week	0.5 mg/week	Yes	5	Yes
4	Cabergoline	1 mg/week	1 mg/week	Yes	85	Yes
5	Cabergoline	1.5 mg/week	1.5 mg/week	Yes	23	Yes
6	Quinagolide	150 mcg/day	150 mcg/day	Yes	78	Yes
7	Cabergoline	0.5 mg/week	0.5 mg/week	Yes	8	Yes
8	Cabergoline	1 mg/week	1 mg/week	Yes	139	Yes
9	Cabergoline	1.5 mg/week	0.5 mg/week	Yes	185	Yes
10	Cabergoline	1 mg/week	1 mg/week	Yes	222	Yes
11	Bromocriptine	7.5 mg/day	7.5 mg/day	Yes	183	Yes
12	Cabergoline	0.25 mg/week	0.25 mg/week	Yes	68	Yes
13	Cabergoline	2 mg/week	1 mg/week	Yes	138	Yes
14	Cabergoline	0.25 mg/week	0.25 mg/week	Yes	98	Yes
15	Cabergoline	3 mg/week	3 mg/week	No*	138	Yes
16	Bromocriptine	2.5 mg/day	2.5 mg/day	Yes	15	Yes
17	Cabergoline	1 mg/week	0.25 mg/week	Yes	145	Yes

* Latest PRL 1147 mU/L (reference range 100-500).