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Prolactinoma management: predictors of remission and recurrence after dopamine agonists withdrawal

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Abstract
Objective Prolactinomas are the most common functional pituitary tumour. Dopamine agonists (DA) are its principal treatment. The criteria that should guide therapy withdrawal and the factors that influence disease remission or relapse are not yet fully established. Our purpose is to evaluate the proportion of patients who attempted DA withdrawal, and to identify the factors that influence clinicians to try it. In addition, we aim to study the factors that are involved in prolactinoma remission/relapse after therapy withdrawal.
Methods We retrospectively evaluated 142 patients with prolactinoma diagnosis who had been treated exclusively with DA. Firstly, the patients were divided in two groups, according to whether DA withdrawal had been attempted, or not, and the factors that might predict clinicians' decision to discontinue the therapy were then analysed. Secondly, patients who attempted withdrawal were further divided into two subgroups, based on their remission or relapse *status* and predictors of remission were evaluated.
Results DA withdrawal was attempted in 35.2% of our patients. Females, subjects with lower initial serum prolactin (PRL) levels, those with microadenomas and those with longer treatment duration all had a higher probability of seeing their therapy discontinued. In the withdrawal group, the remission rate was 72%. Macroprolactinomas relapse more often than microprolactinomas ($p < 0.05$). The recurrence group had higher median initial serum PRL levels and a lower mean duration of therapy, however these variables did not reach statistical significance.
Conclusion We found a low percentage of attempt of withdrawal of DA therapy in the subjects with prolactinoma. Our data confirms that DA therapy can be discontinued with a high remission rate. Tumour size was the main variable that affected the withdrawal outcome in our patients.

Keywords Prolactinoma · Dopamine agonist · Cabergoline · Bromocriptine · Withdrawal · Recurrence · Remission

Introduction

Prolactinomas are the most common functional pituitary tumours and they represent nearly 40% of all adenomas of the pituitary gland, with an estimated prevalence of 100 per million population [1]. Their occurrence differs with age and gender. They are more common in females between 20 and 34 years-old, with an incidence rate in this group of 23.9 per 100,000 person-years [2, 3]. After the fifth decade of life, the incidence of prolactinomas is similar between men and women [1].

The clinical presentation of prolactinoma comprises manifestations related to elevated serum prolactin (PRL), such as galactorrhoea, gonadal and sexual dysfunction (reduced fertility, menstrual disturbance in women and erectile dysfunction in men) and symptoms related to

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tumour expansion, such as headaches and visual disturbances [4].

Dopamine agonists (DA) have become generally recognized as the first line therapy for hyperprolactinemia [5]. DA are ligands of the G protein-type pituitary D2 receptor, negatively coupled to adenylate cyclase. Its activation inhibits PRL gene expression and lactotroph metabolism, leading to reduction in PRL synthesis and release, as well as to tumour shrinkage [6].

Prolactinoma´s treatment is aimed at: (1) normalisation of PRL serum level and control of the related clinical symptoms; (2) reduction of tumour bulk, decreasing visual field defects, cranial nerve dysfunction and hypopituitarism; (3) preservation of normal pituitary function; (4) prevention of recurrence or progression, and; (5) improvement of quality of life [1, 2].

The most commonly used DA are bromocriptine and cabergoline [2]. DA have a wide range of pharmacological actions at different receptor sites. Therefore, these drugs display several effects [2]. The long-term use of DA may increase the risk of pulmonary, retroperitoneal and pericardial fibrotic reactions. A recent study has shown an association between the use of cabergoline in patients with Parkinson´s disease (PD) and cardiac valve abnormalities. Although the doses of DA used in PD are generally significantly higher than those used in prolactinomas, the duration of the treatment in patients with prolactinomas can be much longer, resulting in high cumulative doses [7]. These side effects, together with economic reasons, emphasise the importance of determining the optimal duration of DA therapy for patients with prolactinomas [5]. Treatment may induce the disappearance of the tumour and normoprolactinemia even after its discontinuation thus obviating lifelong treatment [7].

The practice of attempting withdrawal of DA therapy in prolactinomas is recommended, however there is little evidence to sustain this recommendation for withdrawal [7]. The 2006 Pituitary Society guidelines [8] state that if a patient has normal PRL levels after therapy with dopamine agonists for at least 3 years and the tumour volume is markedly reduced, a trial of tapering and discontinuation of these drugs may be initiated. The 2011 Endocrine Society guidelines on the other hand [9] state that DA therapy may be discontinued in patients who have been treated with DA for at least 2 years, who no longer have elevated serum PRL and who have no visible tumour remnant on MRI, provided that they have a clinical and biochemical follow-up [10]. However, the 2006 guidelines were mainly based on one study by Colao et al. and the 2011 guidelines were based on just four studies [5, 10–13]. According to Hu et al., up until 2007, the recurrence rate of hyperprolactinemia after withdrawal of DA varies from 25 to 100% [10]. This wide range of recurrence rates among different authors emphasise that conditions for deciding to attempt DA withdrawal are not standardised, and thus need to be clarified.

The purpose of our study is to determine the proportion of patients for whom DA withdrawal was attempted, and to determine the factors that influence clinicians to attempt this withdrawal. Additionally, we also aim to evaluate the proportion of patients with persistent remission and relapse after DA withdrawal, and to identify the factors that might be associated with either outcome.

Subjects and methods

One hundred forty-two patients with prolactinoma who had been followed at our outpatient clinic from 1986 until 2016 were retrospectively evaluated. Patients' data were extracted from the department´s electronic database and paper files.

The diagnosis of prolactinoma was based on a serum PRL level above the normal range, coupled with a pituitary lesion consistent with a prolactinoma in a magnetic resonance imaging (MRI). Our cohort includes subjects who had been treated exclusively with DA. We excluded patients who received surgical treatment or radiotherapy, and those for whom DA treatment had been stopped due to pregnancy. We only considered the withdrawals of patients who had stopped taking the medication under medical advice. Recurrence of prolactinoma after the discontinuation of DA therapy was defined by a serum PRL level greater than the upper limit of the normal range, together with the necessity to restart the DA therapy.

Firstly, the patients were divided in two groups, according to the decision of their clinician to attempt DA withdrawal, or not. These two groups were compared with regards to gender, age, initial PRL levels, type of DA used, DA initial dose, treatment duration and prolactinoma's diameter at the time of diagnosis, classified as microprolactinoma or macroprolactinoma. Secondly, patients for whom DA withdrawal was attempted were further divided, according to remission or relapse of prolactinoma. These groups were then compared with regards to the same characteristics above, as well as PRL levels at the time of withdrawal, DA dose at the time of withdrawal and duration of treatment until suspension.

Categorical variables were expressed as frequencies and percentages, and were compared by Chi square test. Continuous variables were presented as means and standard deviations, or median and interquartile range (IQR), and the comparison was performed using Student's t test, or the Mann–Whitney test, respectively. Normal distribution was evaluated using the Shapiro–Wilk test, or skewness and kurtosis. Pearson's correlation coefficient was used to assess association between continuous variables. Reported

p values are two-tailed, and $p < 0.05$ was considered significant. Analyses were performed with SPSS Statistics 23®.

Results

The baseline characteristics of patients at the diagnosis are described in Table 1. 142 patients (115 women and 27 men) with a mean age of 37.3 ± 12.7 years were studied. At the initial assessment, the median PRL level was 127 ng/mL (IQR 83.2–345). 96 (67.6%) were microadenomas and 46 (32.4%) were macroadenomas. 105 patients (73.9%) began their treatment with bromocriptine, while 37 (26.1%) began with cabergoline.

Patients with macroprolactinomas presented higher PRL serum levels than patients with smaller tumours [521 (200–1855) vs. 93.3 ng/mL (75.7–138); $p < 0.001$]. Male patients presented an increased proportion of macroprolactinomas when compared to females [OR 6.2; confidence interval (CI) 2.51–15.4; $p < 0.001$]. Clinicians initiated higher doses of bromocriptine ($r = 0.449$; $p < 0.001$) and cabergoline ($r = 0.331$; $p < 0.05$) in patients with higher initial levels of prolactin (data not shown in the table).

Table 2 compares the clinical characteristics of subjects for whom DA withdrawal was attempted with those for whom the clinician decided to maintain the therapy. DA cessation was decided in 50 (35.2%) patients. Females (OR 2.82; CI 1.01–7.69; $p < 0.05$), patients with lower initial serum PRL levels (102 vs. 162 ng/mL; $p < 0.05$), patients with microadenomas (RR 3.03; CI 1.41–7.14; $p < 0.01$) and subjects treated for a longer period (9.86 vs. 6.98 years; $p < 0.05$) had a higher chance of seeing their therapy discontinued by their clinicians. Patients' age at diagnosis ($p = 0.09$), the DA used (RR 0.72; CI 0.39–1.61; $p = 0.42$) and their initial dose ($p = 0.19$ for bromocriptine and $p = 0.61$ for cabergoline) had no impact on the clinician's decision to withdrawal therapy.

Table 3 illustrates the clinical factors that can predict disease remission or relapse. The remission rate in our study population was 72%. Macroprolactinomas tend to recur more frequently than microprolactinomas (OR 4.44; CI 1.10–20.1; $p < 0.05$). Patients with recurrence had a higher median initial serum PRL level and a lower mean duration of therapy, however these variable did not reach statistical significance ($p = 0.16$ and $p = 0.17$, respectively). Gender, age at diagnosis, PRL level at withdrawal, the DA used, their initial and final doses and pregnancy after the withdrawal of DA were not found to be significantly associated with the withdrawal outcome.

Regarding the other pituitary axis, we have data on 26 of the patients that did not have recurrence of prolactinoma after DA withdrawal, 25 females and one male. Two patients had primary hypothyroidism before DA withdrawal

Table 1 Basal clinical characteristics of the study population

Study population [*n*]	142
Female gender [n (%)]	115 (81)
Mean age at diagnosis [years (±SD)]	37.3 (±12.7)
Prolactin level at diagnosis [ng/mL, median (IQR)]	127 (83.2–345)
Macroadenomas [n (%)]	46 (32.4)
Treated with bromocriptine [n (%)]	105 (73.9)
Initial dose [mg per week, median (IQR)]	35 (17.5–52.5)
Treated with cabergoline [n (%)]	37 (26.1)
Initial dose [mg per week, median (IQR)]	0.5 (0.5–1.0)

Table 2 Comparison between patients who underwent dopamine agonist withdrawal, and those for whom the therapy was maintained

	Withdrawal	No withdrawal	*p* value
Patients [n (%)]	50 (35.2)	92 (64.8)	–
Gender [n (%)]			<0.05
Female	45 (39.1)	70 (60.9)	
Male	5 (18.5)	22 (81.5)	
Age at diagnosis [years, mean (±SD)]	35.1 (±10.3)	38.5 (±13.8)	0.09
Prolactin level at diagnosis [ng/mL, median (IQR)]	102 (76.8–187)	162 (85.3–487)	<0.05
Initial diameter			<0.01
Microadenoma [n (%)]	41 (42.7)	55 (57.3)	
Macroadenoma [n (%)]	9 (19.6)	37 (80.4)	
Dopaminergic agonist			0.42
Bromocriptine [n (%)]	39 (37.1)	66 (62.9)	
Cabergoline [n (%)]	11 (29.7)	26 (70.3)	
Bromocriptine initial dose [mg per week, median (IQR)]	35 (17.5–35)	35 (17.5–52.5)	0.19
Cabergoline initial dose [mg per week, mg per week, median (IQR)]	0.5 (0.5–0.5)	0.5 (0.5–1)	0.61
Duration of treatment [years, mean (±SD)]	9.86 (±7.07)	6.98 (±5.71)	<0.05

Table 3 Characteristics of subjects in the relapse and remission groups

	Relapse	Remission	*p* value
Patients [n (%)]	14 (28.0)	36 (72.0)	–
Gender [n (%)]			0.53
Female	12 (26.7)	33 (73.3)	
Male	2 (40.0)	3 (60.0)	
Age at diagnosis [years, mean (±SD)]	36.1 ± 13.0	34.6 ± 9.2	0.65
Prolactin level at diagnosis [ng/mL, median (IQR)]	128 (84.2–471)	100 (77.1–148)	0.16
Prolactin level at withdrawal [ng/mL, median (IQR)]	8.9 (4.1–373.3)	11.1 (4–21)	0.92
Initial diameter			<0.05
Microadenoma [n (%)]	9 (22.0)	32 (78.0)	
Macroadenoma [n (%)]	5 (55.6)	4 (44.4)	
Dopaminergic agonist			0.41
Bromocriptine [n (%)]	12 (30.8)	27 (69.2)	
Cabergoline [n (%)]	2 (18.2)	9 (81.8)	
Bromocriptine initial dose [mg per week, median (IQR)]	35 (17.5–48.1)	35 (17.5–35)	0.88
Cabergoline initial dose [mg per week, median (IQR)]	0.5 (0.5–0.5)	0.5 (0.5–0.75)	1.00
Bromocriptine final dose [mg per week, median (IQR)]	17.5 (8.75–17.5)	17.5 (17.5–17.5)	0.05
Cabergoline final dose [mg per week, mg per week, median (IQR)]	0.5 (0.25–0.5)	0.25 (0.25–0.5)	0.52
Duration of treatment [years, mean (±SD)]	8.1 ± 4.5	10.6 ± 7.8	0.17
Pregnancy [n (%)]			0.73
Yes	21 (75.0)	7 (25.0)	
No	12 (70.6)	5 (29.4)	

and maintained the treatment for hypothyroidism initiated previously after DA withdrawal. One patient was already being treated with methylprednisolone for other reason before DA withdrawal and also maintained the treatment after DA withdrawal. When clinically suspected, gonadal, adrenal and thyroid function was evaluated. Two females had postmenopausal hypogonadism. One male and two females showed recovery of gonadal function even after DA withdrawal. No adrenal insufficiency was diagnosed or treated.

Discussion

Dopamine agonists withdrawal

The latest guidelines on the management of prolactinomas from the Endocrine Society suggest that with close clinical and biochemical follow-up, therapy may be discontinued in patients who: (1) have been treated with DA for at least 2 years; (2) no longer have hyperprolactinemia; (3) who have no visible tumour on MRI [9]. We analysed our data to determine whether DA therapy is withdrawn frequently, or not. We have found a percentage of withdrawal of 35.2%. According to a recent survey, around 20% of UK endocrinologists do not routinely withdraw agonist therapy when managing microprolactinomas [14]. Referring only to microprolactinomas, we found a percentage of 42.7% of DA withdrawal.

We also analysed some clinical, analytic and imagiological variables to evaluate which are the patients for whom clinicians' tend to discontinue therapy more easily. This topic has not been studied in depth before. In our study, females had three times the chance of therapy discontinuation than males. Patients with microadenomas also had three times the chance of seeing their therapy interrupted when compared with those with tumours larger than 1 cm. Almost half of the subjects with microprolactinoma had their therapy discontinued, as opposed to just 19.6% of the subjects with macroprolactinoma.

Lower prolactin levels and longer therapy duration were variables that also impacted on clinicians' decision. There is a lot of controversy regarding the duration of DA therapy. While some studies suggest 1 year of DA therapy before withdrawal, others suggest as long as 6 years of treatment. In a survey of British endocrinologists, 41.2% of clinicians withdraw the treatment after 3 years [14]. In our study, we concluded that the mean duration of treatment for the withdrawal group was 9.86 years, while the mean duration of treatment in the group of patients who did not attempt withdrawal was 6.98 years. This suggests that in our centre, clinicians need a longer duration of treatment to feel confident to attempt withdrawal.

On the contrary, age did not influence the decision of withdrawal, which is in accordance with other studies which showed zero impact of patients' age on the disease outcome after withdrawal [15]. The DA used and their doses had no influence on the decision of withdrawal.

Remission/relapse after the withdrawal

In this study, we were able to demonstrate that 72% of the patients persisted in remission after DA withdrawal. In microprolactinomas, the remission rate was 78%, and in macroprolactinomas it was 44.4%. This is a significantly higher proportion of patients in remission when compared to previous studies. A publication by Colao et al. in 2004 stated that 67% of the microprolactinomas, and 57% of the macroprolactinomas persisted in remission after DA withdrawal [12]. In a more recent study, also by Colao and colleagues, the remission rates were 66.1 and 46.9% for microprolactinomas and macroprolactinomas respectively [16]. These results suggest that a considerable proportion of patients can have their therapy successfully discontinued, as long as they accomplish some clinical criteria, such as the disappearance of tumour on a MRI, and a prolonged period of normal serum PRL during treatment. The first study to test the 2006 Pituitary Society recommendations [5] reported an estimated 18-month persistence in remission of 37% in a cohort of 46 selected patients with normal PRL levels treated with cabergoline for at least 2 years. Later, Dekkers et al. [13] found that the proportion of patients that persisted in remission following DA withdrawal was 21% for microprolactinomas, and 16% for macroprolactinomas, which is a much higher recurrence rate than those reported by Colao and also in our study.

Regarding those factors that may influence remission or relapse, in our study, gender has shown to have no effect on this outcome. Most of the studies in the literature are in agreement with our findings [6, 7, 11, 17]. Exceptions include one study by Colao et al., which reported higher recurrence rates in males [16]. The doubt about potentially more aggressive prolactinomas in men has been raised before [18], however it has been demonstrated that prolactinomas in men also have a successful response to long-term cabergoline treatment. Nevertheless, since men have macroprolactinomas more often [19], as confirmed in our study, this could be a partial explanation for a higher recurrence rate of hyperprolactinemia after cabergoline withdrawal in men in Colao´s study.

We found no correlation between age at diagnosis and remission rates. This is also in accordance with earlier studies [6, 7, 11, 12, 17].

Patients with a higher initial serum PRL level at diagnosis seemed to have higher chances of recurrence, although this variable did not reach statistical significance. This relation between baseline PRL concentration and risk of relapse has been observed in previous studies [4, 11, 12, 15, 16]. However, conflicting studies did not confirm our results [5–7, 10, 17].

There was no significant difference is the median serum level of PRL at withdrawal between the patients in the remission group and the patients in the relapse one. However, earlier studies came to different conclusions. Barber et al. observed that following DA discontinuation, those patients with higher serum PRL levels at the moment of withdrawal were most likely to have recurrence of hyperprolactinemia [4]. Kharlip et al. found a relationship between PRL nadir and risk of recurrence [5].

In our study, the chosen dopaminergic agent did not have an impact on the withdrawal outcome. Prospective studies comparing bromocriptine and cabergoline are lacking, however previous retrospective studies have reported results in accordance with our data [4, 7, 11, 17], yet others disagree and suggest that remission rates are significantly higher in patients treated with cabergoline [1, 14, 15]. Remission rates with bromocriptine range from 7 to 44%, whereas remission rates with cabergoline vary from 17 to 46%, or even 69% if only microprolactinomas are taken into account [17]. However a selection bias may be interfering in these results, as a potential Type 2 error, as bromocriptine may be used more frequently with more responsive and tolerant patients.

There was no significant association between bromocriptine and cabergoline initial doses and the rate of recurrence. Few studies have analysed this variable, however the results of Passos et al. are in accordance with our data [6]. We also found no significant association between bromocriptine and cabergoline doses at withdrawal and risk of recurrence. Previous studies are in accordance with our results [5, 7], however, Hu et al. found different results, suggesting that under the premise of maintaining normoprolactinemia, patients with reduced cabergoline intake to the lowest dose before withdrawal had a lower recurrence rate than patients taking higher cabergoline doses at the time of withdrawal [10].

In our study, patients with lower treatment duration had higher chances of recurrence, although this variable did not reach statistical significance. Some studies suggest marked differences in tumour regrowth after bromocriptine withdrawal, depending on treatment duration. Tindall et al. [20] and Basseti et al. [21] suggested that a short treatment with bromocriptine, during 4–6 weeks, causes "cytostatic" effects, such as reduction in organelle size and reversible diminution of the volume of prolactin cells. On the other hand, Landolt and Osterwalder reported the development of perivascular fibrosis in tumour cells after long treatment and they proposed that these effects may be the cause of remission [22]. Dekkers et al. showed that treatment

longer than 2 years is related with a better outcome [13]. A prospective study by Huda et al. [7] demonstrated that longer duration of treatment is a strong predictor of remission, as well as that of Colao et al. [16], which also stated that longer duration of therapy was a significant predictor of remission. A retrospective study from 2016 also confirmed these findings [15]. However, Hu et al. [10] published a meta-analysis in which a significant association between lower recurrence and longer therapy duration was not found, suggesting that treatment for more than 2 years is not a positive indicator for cabergoline withdrawal. This finding is in accordance with other studies that also suggested that a longer length of therapy is not associated with higher remission rates [5, 6, 11, 17]. In older retrospective studies, the treatment duration varied considerably from 12 to 58.8 months [7]. The average duration of therapy in our study was longer than that of previous studies, and this may have influenced our results.

We showed higher remission rates in patients with microprolactinoma than in those with macroprolactinoma. ($p < 0.05$) Other studies have underlined the impact of tumour size on recurrence rates [4, 12]. However, Kharlip et al. found no association between initial tumour size and the outcome after withdrawal [5].

Pregnancy is another factor that has been implicated in recurrence rates. We have found no relationship between remission and pregnancy after the withdrawal of DA in our study. However, Jeffcoate et al. followed women with prolactinomas during 15 years and reported that there was a higher percentage of remission in the group of women that became pregnant, compared to the group of women who did not (35 vs. 14%) [23].

Natural history is another component that might also have an effect on prolactinomas evolution, despite the need to clarify the mechanisms involved. Koppelman et al. followed 25 women with untreated prolactinomas (18 micro and 7 macroprolactinomas) for a mean period of 11.3 years. Amenorrhea was resolved spontaneously in 7 of 22 patients, while 8 of 19 patients had galactorrhoea that was completely resolved. At the re-evaluation, mean PRL level was reduced from 225 to 155 μg/L. Only one patient had a progression of the sellar bulk [24]. Sisam et al. [25] followed a group of 38 patients with untreated microprolactinomas during 31 months and reported that approximately 55% of them presented normalisation of PRL levels, and there was no prolactinoma regrowth. Jeffcoate et al. [23] studied women with hyperprolactinemia (macroprolactinomas excluded) during a follow-up period of 15 years, and reported that 33% showed normalisation of PRL levels without treatment.

Our study has some limitations, namely: (1) we cannot assure that patients without recurrence will never relapse, and this can result in an underestimation of recurrence, and; (2) the relative small number of patients that attempted withdrawal, which limits comparisons between remission and relapse groups.

To clearly define the optimal DA withdrawal strategy, large prospective studies are necessary, in order to make the comparison of withdrawal outcomes possible in patients selected according to different criteria.

Conclusion

In our study, we found a low percentage (35.2%) of withdrawal of DA therapy in subjects with prolactinoma. Females, microprolactinomas, patients with lower initial serum PRL levels and with longer therapy duration all had a higher probability of seeing their therapy discontinued.

Our data suggests that DA therapy may be discontinued with a high remission rate. We observed that 72% of the patients persisted in remission after DA therapy withdrawal. In microprolactinomas, the remission rate was even higher (78%). Accordingly, tumour size was the main variable that affected withdrawal outcome in our patients. Lower median initial PRL levels and longer duration of treatment seem to be associated with higher rates of remission, however these variables did not reach statistical significance.

Earlier published studies on the recurrence of hyperprolactinemia following DA withdrawal in patients with prolactinoma showed higher recurrence rates compared to our study. This may be explained by the longer duration of treatment in our study. The Endocrine Society guidelines state that with careful follow-up, DA withdrawal may be attempted in patients that have been treated for at least 2 years. On account of our higher remission rate, we suggest studying a longer therapy duration before trying DA withdrawal.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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