ORIGINAL ARTICLE

Withdrawal of Long-Term Cabergoline Therapy for Tumoral and Nontumoral Hyperprolactinemia

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ABSTRACT

BACKGROUND

Whether the withdrawal of treatment in patients with nontumoral hyperprolactinemia, microprolactinomas, or macroprolactinomas is safe and effective has been unclear. We performed an observational, prospective study of cabergoline (a dopamine-receptor agonist) withdrawal in such patients.

METHODS

The study population included 200 patients — 25 patients with nontumoral hyperprolactinemia, 105 with microprolactinomas, and 70 with macroprolactinomas. Withdrawal of cabergoline was considered if prolactin levels were normal, magnetic resonance imaging (MRI) showed no tumor (or tumor reduction of 50 percent or more, with the tumor at a distance of more than 5 mm from the optic chiasm, and no invasion of the cavernous sinuses or other critical areas), and if follow-up after withdrawal could be continued for at least 24 months.

RESULTS

Recurrence rates two to five years after the withdrawal of cabergoline were 24 percent in patients with nontumoral hyperprolactinemia, 31 percent in patients with microprolactinomas, and 36 percent in patients; with macroprolactinomas. Renewed tumor growth did not occur in any patient; in 10 female patients (22 percent) and 7 male patients (39 percent) with recurrent hyperprolactinemia, gonadal dysfunction redeveloped. In all diagnostic groups, prolactin levels at the time of recurrence were significantly lower than at diagnosis ($P<0.001$). The Kaplan–Meier estimated rate of recurrence at five years was higher among patients with macroprolactinomas and those with microprolactinomas who had small remnant tumors visible on MRI at the time of treatment withdrawal than among patients whose MRI scans showed no evidence of tumor at the time of withdrawal (patients with macroprolactinomas, 78 percent vs. 33 percent, $P=0.001$; patients with microprolactinomas, 42 percent vs. 26 percent, $P=0.02$).

CONCLUSIONS

Cabergoline can be safely withdrawn in patients with normalized prolactin levels and no evidence of tumor. However, because the length of follow-up in our study was insufficient to rule out a delayed increase in the size of the tumor, we suggest that patients be closely monitored, particularly those with macroprolactinomas, in whom renewed growth of the tumor may compromise vision.

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Prolactinoma, which is the most common type of pituitary tumor, has an estimated prevalence of 100 per 1 million persons. In most cases, medical therapy with dopamine agonists normalizes the level of prolactin, restores gonadal function and fertility, and substantially reduces the size of the tumor.[1,2] Bromocriptine (at a dose of 2.5 to 15 mg daily) has been the traditional drug used to manage prolactinoma[3-5]; it normalizes prolactin levels in 80 to 90 percent of patients with microprolactinomas and in approximately 70 percent of those with macroprolactinomas, decreases the size of the tumor, and improves visual-field defects. However, bromocriptine often has side effects that may prevent the administration of therapeutic doses.[6] Cabergoline, a selective dopamine D2-receptor agonist with long-lasting action has been used as a highly effective treatment for microprolactinoma and macroprolactinoma.[7-10] The side effects of cabergoline appear to be less frequent and less severe than those of bromocriptine.[7,10] Primary cabergoline treatment has been associated with greater tumor shrinkage than has primary therapy with other dopamine agonists.[10] In patients with microprolactinomas or macroprolactinomas who were treated primarily with either bromocriptine or cabergoline, cabergoline appeared to be superior in normalizing prolactin levels, restoring gonadal function, and decreasing the size of the tumor.[11]

There is wide consensus that primary medical treatment of prolactinoma with dopamine agonists is preferable to surgery, not only because of the excellent clinical results of medical therapy but also because of the risk of recurrent hyperprolactinemia after unsuccessful surgery.[12-14] A definitive cure of these tumors is considered possible, however, only with surgery or, in rare cases, with surgery plus radiation therapy.[2] The results of withdrawal of medical therapy, based on scanty data obtained from small patient cohorts that were followed for short periods, have indicated that hyperprolactinemia recurs more often when treatment is withdrawn than when surgery is performed — for a rate of approximately 90 percent in patients with macroprolactinomas and 80 percent in patients with microprolactinomas.[15-21] Renewed growth of the tumor appears to be uncommon but may occur after some delay and with a risk of compromised vision.[15-21] To our knowledge, no systematic studies have investigated the effect of cabergoline withdrawal on rates of remission of prolactinoma, although preliminary reports have indicated that in 17 to 30 percent of patients, the levels of prolactin are in the normal range one year after the withdrawal of cabergoline.[22,23] We report the results of a prospective study of cabergoline withdrawal in patients who were treated primarily with this compound.

METHODS

INCLUSION CRITERIA

Patients were eligible for our study if after treatment with cabergoline they had serum prolactin levels that were in the normal range and the tumor had disappeared or decreased in size by 50 percent or more from base line. Patients were considered for withdrawal of cabergoline only if the outer border of the tumor was 5 mm or more from the optic chiasm, without magnetic resonance imaging (MRI) evidence of invasion of one or both cavernous sinuses or any other critical area. Patients were required to continue follow-up after withdrawal for at least 24 months. To minimize the risk of errors in reading MRI scans, all patients continued to receive cabergoline therapy for 12 months after fulfilling the withdrawal criteria and before withdrawal of the medication. The study was approved by the ethics committee of Federico II University of Naples. All patients provided informed consent. In the period from 1994 to 1997, oral consent was obtained in the presence of a third party, and after 1997, written consent was obtained. All procedures were performed in accordance with the standard approach used to treat prolactinoma at Federico II University Hospital.

PATIENTS

From January 1, 1994, through December 31, 1998, 354 patients (283 women and 71 men) in whom hyperprolactinemia was newly diagnosed received cabergoline as first-line therapy (194 patients with microprolactinomas, 135 patients with macroprolactinomas, and 25 patients with nontumoral hyperprolactinemia) (Fig. 1). Subsequently, treatment was stopped in 57 patients (16 percent) because of pregnancy. Prolactin levels normalized in 273 of the remaining 297 patients (92 percent); 200 of these 273 patients (73 percent, 56 percent of the study cohort) fulfilled the criteria for cabergoline withdrawal and were included in the study (Table 1). Diagnostic criteria for macroprolactinoma were serum prolactin levels of 200 μg per liter or more and evidence on MRI of a pituitary tumor that was more than 10 mm in diameter. For microprolactinoma, the criteria were serum prolactin levels of 50 μg

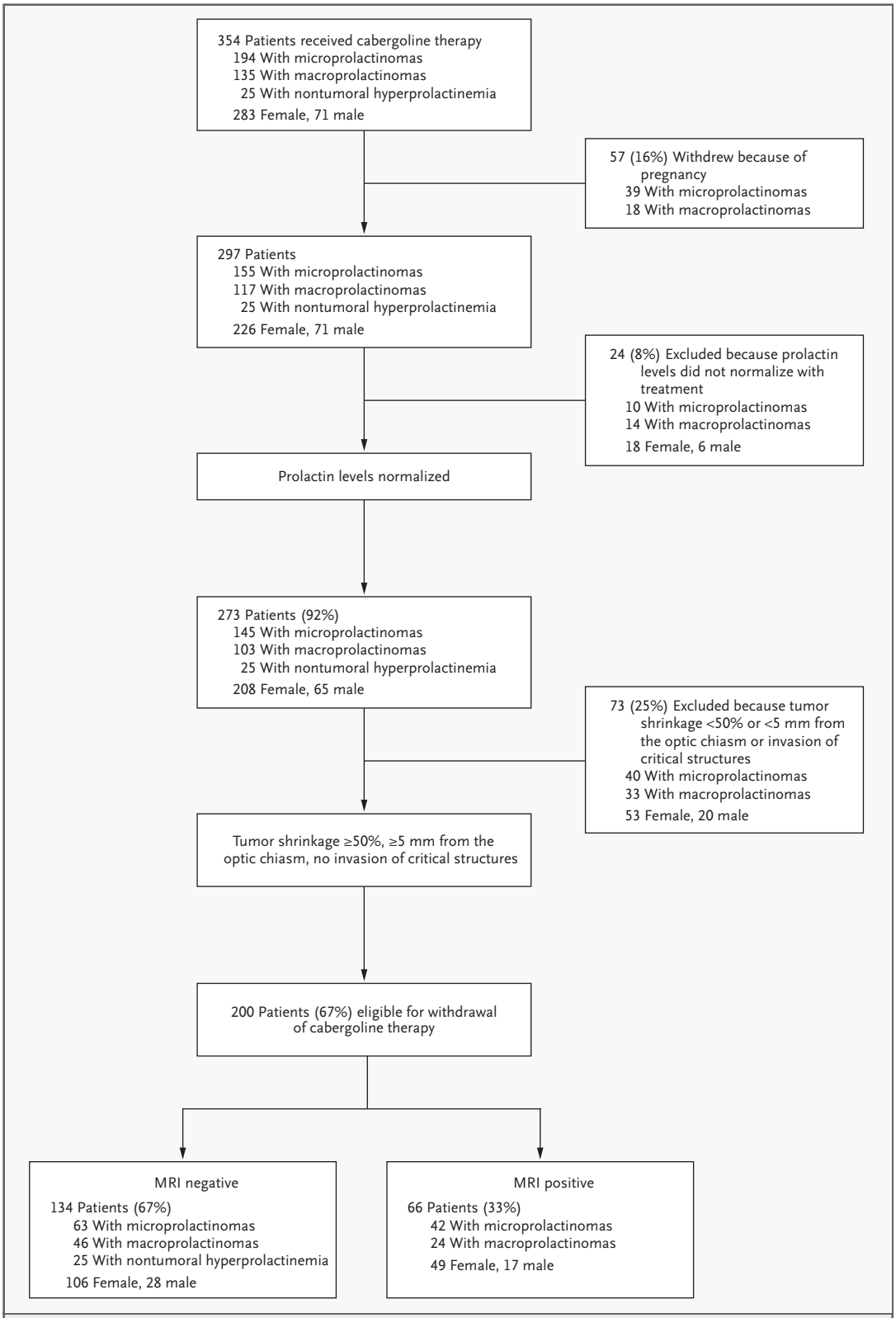

Figure 1. Patient Population at Study Entry.

Table 1. Base-Line Characteristics of 200 Patients Eligible for Withdrawal of Cabergoline.*

Characteristic	Nontumoral Hyperprolactinemia (N=25)	Microprolactinomas (N=105)	Macroprolactinomas (N=70)	P Value
Sex (no. of patients)				
Female	25	94	37	
Male	0	11	33	
Age (yr)				
Median	28†	30†	40	<0.001
Range	18–55†	15–66†	19–70	<0.001
Prolactin (μg/liter)				
Base line	68.5±10.1†	162.2±48.2†	915.6±1413	<0.001
Nadir with cabergoline	3.6±3.8‡	6.0±5.2	5.3±3.0	0.04
Prolactin suppression (%)	94.6±5.7†	96.2±5.1†	98.9±0.8	<0.001
Maximal tumor diameter (mm)				
Base line	—	6.9±1.6	17.1±6.4	<0.001
Smallest	—	1.2±1.6	2.3±3.3	0.08
Duration of cabergoline treatment (mo)				
Median	36	48	42	0.11
Range	24–50	24–75	24–72	0.11
Cabergoline dose (mg/wk)				
Median	0.5§	1	1	<0.001
Range	0.25–1§	0.5–3.5	1–2	<0.001

* Plus–minus values are means ±SD. P values are for comparison of the three groups by analysis of variance.
† P<0.001 for the comparison with the macroprolactinoma group.
‡ P=0.03 for the comparison with the microprolactinoma group.
§ P<0.001 for the comparison with the microprolactinoma and macroprolactinoma groups.

per liter or more and evidence on MRI of a pituitary tumor that was 10 mm or less in diameter. For nontumoral hyperprolactinemia, the criteria were serum prolactin levels above the normal range and evidence on MRI of a normal pituitary, without another explanation for an increased prolactin level, such as primary hypothyroidism or drug-induced hyperprolactinemia.[24] No patient with nontumoral hyperprolactinemia or a microprolactinoma and only 31 of 103 (30 percent) of those with macroprolactinomas had panhypopituitarism. All male patients had a history of decreased libido and impaired sexual potency, and all female patients had a history of menstrual disturbances. Of 208 female patients, 111 (53 percent) had spontaneous or expressible galactorrhea. Of 103 patients with macroprolactinomas, 39 (38 percent) had visual-field defects, and visual loss occurred in 4 of these patients (10 percent).

TREATMENT PROTOCOL

Cabergoline was administered orally at a single starting dose of 0.5 mg in the first week and then at a dose of 0.5 mg twice per week. After two months of treatment, the dose was adjusted every two months on the basis of suppression of serum prolactin. The dose of cabergoline was increased to 5 to 7 mg per week in patients in whom prolactin levels did not normalize[11] and was reduced in patients in whom the prolactin levels declined to less than 5 μg per liter. Before the withdrawal of cabergoline, the dose was reduced to 0.5 mg per week in all patients; cabergoline was withdrawn only in patients whose prolactin levels remained normal after dose reduction.

STUDY PROTOCOL

The few patients who had hypopituitarism received standard replacement therapy with recombinant human growth hormone (5 to 8 μg per kilogram of body weight per day subcutaneously), levothyroxine (50 to 100 μg orally per day), cortisone acetate (25 to 37.5 mg orally per day), and either estrogen–progestin (orally each day) or testosterone (250 mg by intramuscular injection monthly), as necessary.[11] Serum insulin-like growth factor I, free thyroid hormone, and testosterone and serum and urinary sodium and potassium were measured periodically to assess the adequacy of the hormone-replacement

therapy. At the time of enrollment, the serum prolactin level was calculated as the average of a 6-hour profile during which blood was sampled every 30 minutes from 8 a.m. to 2 p.m.; prolactin levels were measured at 8, 8:15, and 8:30 in the morning during treatment, and the average value was recorded. Prolactin levels were measured by radioimmunoassay (intraassay and interassay coefficients of variation, 5 percent and 7 percent, respectively; normal range, 5 to 25 μg per liter in women and 5 to 15 μg per liter in men). General clinical examinations were performed throughout follow-up. After the withdrawal of cabergoline, prolactin levels were measured every 15 days during the first month, then once a month for 5 months, quarterly during the second half of the first year, and every 6 months thereafter. This scheme was used for all the study subjects during follow-up, unless there was a recurrence. For patients in whom a recurrence developed, treatment was provided according to our current clinical protocol on the basis of prolactin levels.

DIAGNOSIS OF RECURRENCE

Recurrence was considered to have occurred if prolactin levels were above the normal range. To minimize the risk of renewed symptoms, cabergoline treatment was immediately restarted if clinical symptoms related to hyperprolactinemia reappeared or if repeated measurements of prolactin after 7 to 10 days confirmed hyperprolactinemia. Otherwise, follow-up was continued according to the study protocol.

MRI STUDIES

Tumor mass was evaluated with the use of MRI as previously reported.[10] The MRI studies were performed with clinical 0.5-Tesla scanners from 1994 to 1999, 1-Tesla scanners from 2000 to 2001, and 1.5-Tesla scanners from 2002 on, with the use of T_1-weighted gradient-recalled echo in the sagittal and coronal planes. For each measurement, 7 to 11 slices were obtained, at a thickness of 2 to 3 mm and an in-plane spatial resolution of 0.70 to 0.97 mm. Images were obtained before and after the administration of 0.1 mmol of gadolinium chelate (diethylene-triamine pentacetate). The maximal tumor diameter was calculated in millimeters. The MRI studies were performed before treatment with cabergoline; at 3, 6, and 12 months during the first year of treatment; and then every 6 to 12 months on the basis of the reduction in the size of the tumor. After the withdrawal of cabergoline, MRI was repeated every six months the first year and then yearly. If recurrent hyperprolactinemia was diagnosed, the patient underwent MRI at the time of diagnosis.

OPHTHALMOLOGIC EXAMINATION

All patients with macroprolactinomas underwent testing for visual-field defects with the use of Goldmann–Friedmann perimetry, as well as visual acuity, at base line. The ophthalmologic examination was repeated every six months during cabergoline treatment in patients with visual disturbances. After the withdrawal of cabergoline, two patients were reexamined because of visual abnormalities due to atrophy of the optic nerve, despite the disappearance of tumor during treatment with cabergoline.

STATISTICAL ANALYSIS

Data are reported as means ±SD. Data analysis was performed with the use of SPSS software (SAS Institute). Mean values in the three study groups were compared with the use of paired and unpaired t-tests and analyses of variance. Categorical variables were compared with the use of Fisher's exact test. A Cox proportional-hazards regression analysis was used to determine which variables independently predicted recurrence of hyperprolactinemia, evaluated as the average prolactin value at the last follow-up visit after the withdrawal of cabergoline. We entered into the model only variables that had a P value of less than 0.01 in the univariate analysis. The Kaplan–Meier method was used to analyze the primary end point of recurrent hyperprolactinemia during long-term follow-up. Recurrence-free survival was measured from the date of cabergoline withdrawal to the date of relapse, and the data were censored at the date of the last follow-up visit. The log-rank test was used to compare recurrence-free survival curves. P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

NONTUMORAL HYPERPROLACTINEMIA

In the group of patients with nontumoral hyperprolactinemia, cabergoline was withdrawn after a median treatment period of 36 months at a median dose of 0.5 mg per week (Table 1). Of 25 female patients with nontumoral hyperprolactinemia, 6 (24 percent) had a recurrence after a median of 18 months (Table 2), but in none of them did symptoms reappear. In the remaining 19 of these patients (76 percent), hyperprolactinemia remained

controlled at a median of 48 months after the withdrawal of cabergoline.

MICROPROLACTINOMA

In the group with microprolactinomas, cabergoline was withdrawn after a median treatment period of 48 months at a median dose of 1 mg per week (Table 1). In 63 of 105 patients, MRI studies of the pituitary gland showed no evidence of renewed tumor growth. In the remaining 42 patients, the tumor decreased by 55.5±4.8 percent (from 7.0±1.4 to 3.1±0.6 mm). In 32 patients (30 percent), hyperprolactinemia recurred after a median of 12 months; none of these 32 patients had MRI evidence of recurrent microprolactinomas. In 5 of 25 female patients (20 percent) oligomenorrhea developed; none of the 25 female patients had galactorrhea. Three of seven male patients (43 percent) noted decreases in sexual potency and libido, although their testosterone levels did not change. Hyperprolactinemia remained controlled in the remaining 73 patients (70 percent) at a median of 36 months after the withdrawal of cabergoline.

MACROPROLACTINOMA

In the macroprolactinoma group, cabergoline was withdrawn after a median treatment period of 42 months at a median dose of 1 mg per week (Table 1). Of 70 patients with macroprolactinomas, MRI studies of the pituitary gland in 46 showed no evidence of renewed tumor growth. In the remaining 24 patients, tumor size decreased by 60.7±6.2 percent (from 16.9±4.1 to 6.6±1.6 mm). Twenty-five of the 70 patients (36 percent) had a recurrence of hyperprolactinemia after a median of 18 months; none of these 25 had MRI evidence of recurrent growth of the macroprolactinoma. Of 14 female patients, 5 noted renewed oligomenorrhea (36 percent), and 1 had recurrent galactorrhea (7 percent). Of 11 male patients, 4 (36 percent) reported decreased sexual

Table 2. Characteristics of the Patients According to Whether Hyperprolactinemia Recurred after the Withdrawal of Cabergoline.*

Characteristic	Nontumoral Hyperprolactinemia			Microprolactinomas			Macroprolactinomas		
	Recurrence	No Recurrence	P Value	Recurrence	No Recurrence	P Value	Recurrence	No Recurrence	P Value
Patients — no. (%)	6 (24)	19 (76)		32 (30)	73 (70)		25 (36)	45 (64)	
Sex — no.						0.02			0.74
Female	6	19		25	69		14	23	
Male	0	0		7	4		11	22	
Age — yr									
Range	26–55	18–30	<0.001	19–62	15–66	<0.001	19–70	19–66	0.52
Median	35	28	<0.001	35	28	<0.001	44	50	0.20
Prolactin — μg/liter									
Base line	69.3±5.5	68.3±11.3	0.8	179.3±37.6	154.7±50.6	0.01	935.1±859	904.8±1652	0.93
Nadir with cabergoline	9.8±2.6	1.6±0.8	<0.001	10.1±5.8	4.1±3.6	<0.001	7.3±3.6	4.1±1.9	<0.001
Prolactin suppression — %	85.4±4.6	97.4±0.9	<0.001	94.2±5.0	97.1±5.0	0.005	98.7±1.0	98.9±0.6	0.34
Maximal tumor diameter — mm									
Base line	—	—	—	6.9±1.4	6.8±1.7	0.8	18.4±4.8	16.4±7.1	0.22
Smallest	—	—	—	1.7±1.6	1.0±1.5	0.038	3.7±4.0	1.4±2.5	0.003
Tumor reduction during treatment — %	—	—	—	75.1±23.8	85.2±20.9	0.003	79.9±21.8	90.2±16.6	0.03
Median duration of cabergoline therapy — mo	48	36	0.1	48	36	0.009	48	36	0.01
Maximal dose of cabergoline — mg/wk	0.5±0	0.5±0.2	1	1.6±0.9	1.1±0.6	0.004	1.3±0.4	1.2±0.3	0.19
Average prolactin level at last follow-up visit — μg/liter	44.1±7.0	10.5±4.9	<0.001	48.1±13.1	13.3±4.1	<0.001	54.0±18.4	13.3±4.9	<0.001
Range of follow-up after withdrawal — mo	3–24	24–60	<0.001	3–36	24–60	<0.001	3–30	18–60	<0.001
Median time to recurrence — mo	18	—		12	—		18	—	0.51

* Plus–minus values are means ±SD. P values were calculated with the use of Student's t-test for unpaired (individual) data and the chi-square test or Fisher's exact test for proportions.

potency and decreased libido, which were accompanied by a decrease in testosterone levels (from 4.2±0.5 to 3.2±0.4 μg per liter). In 45 patients (64 percent), hyperprolactinemia remained controlled at a median of 48 months after the withdrawal of cabergoline.

As shown in Table 2, in all three groups, the overall recurrence rate, the median time to recurrence, and the prolactin level at recurrence were similar. The average prolactin level was significantly lower at the last follow-up visit than at diagnosis in all groups (Table 2). The Kaplan–Meier estimate of the five-year recurrence rate was higher among patients with either macroprolactinomas or microprolactinomas who had remnant tumors on MRI before the withdrawal of cabergoline than among those who had no evidence of tumor on MRI (patients with macroprolactinomas, 78 percent vs. 33 percent, P=0.001; patients with microprolactinomas, 42 percent vs. 26 percent, P=0.02) (Fig. 2). Sixty-three patients had recurrent hyperprolactinemia, more than half of them (56 percent) during the first year after the withdrawal of cabergoline, 33 percent during the second year, 11 percent during the third year, and none thereafter (P<0.001).

Recurrences of hyperprolactinemia were not associated with male or female sex (P=0.93) or with the presence of menopause (28 percent of study patients were in premenopause and 36 percent in postmenopause, P=0.50). Age, prolactin levels at base line, nadir prolactin levels, percentage of prolactin suppression, smallest tumor diameter after cabergoline therapy, duration of treatment, and dose of cabergoline were higher in patients with a recurrence than in those in whom persistent control was achieved, though there were some differences among the three groups (Table 2). Cox regression analysis indicated that the maximal diameter of a tumor during cabergoline treatment was the best predictor of the prolactin level at the last follow-up visit after the withdrawal of cabergoline (chi-square=12, P<0.001). The hazard rate for the recurrence of hyperprolactinemia was 19 percent for each millimeter increment in the maximal tumor diameter. Figure 3 summarizes the prevalence of normoprolactinemia after cabergoline withdrawal in different categories of patients.

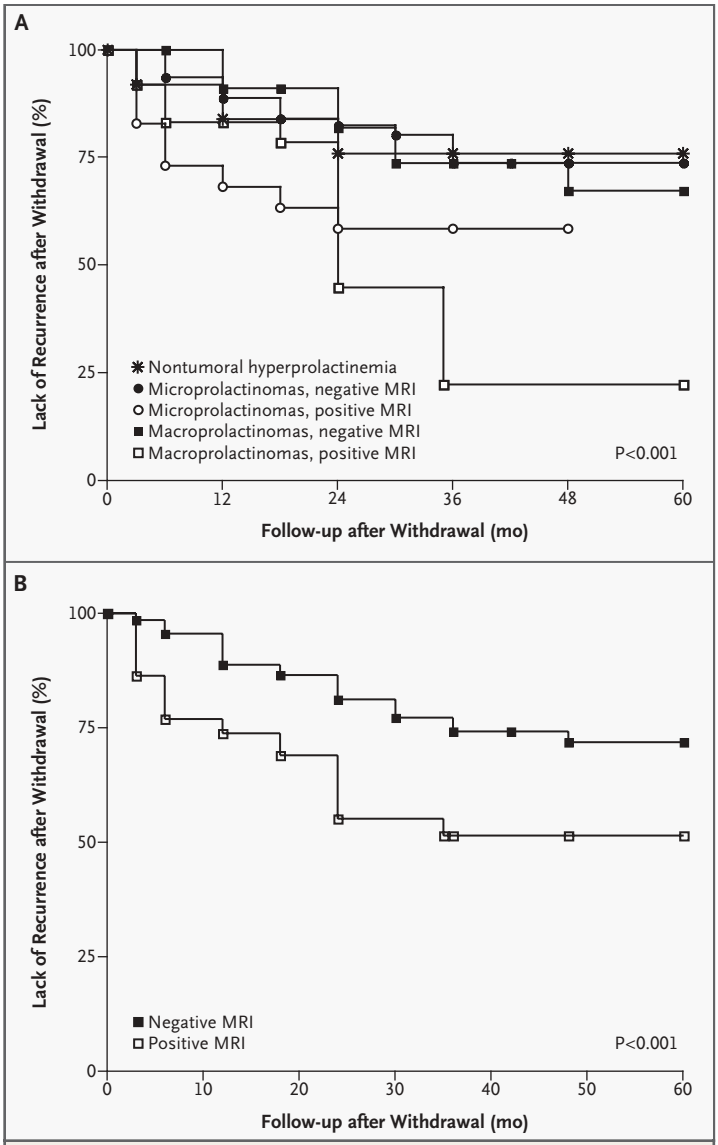

Figure 2. Kaplan–Meier Estimates of Recurrence Rates after 60 Months in the Three Groups of Patients (Panel A) and in the Overall Study Population (Panel B) According to Whether MRI Studies during Treatment Were Positive or Negative.

Panel A shows recurrence rates in 25 patients with nontumoral hyperprolactinemia, 63 patients with microprolactinomas and negative MRI studies, 42 patients with microprolactinomas and persistent abnormalities on MRI, 46 patients with macroprolactinomas and negative MRI studies, and 24 patients with macroprolactinomas and persistent abnormalities on MRI. Panel B shows rates of recurrence in two groups of patients divided on the basis of MRI findings. The first group included the 25 patients with nontumoral hyperprolactinemia and the 63 patients with microprolactinomas and 46 patients with macroprolactinomas who had negative MRI studies. The second group included the 42 patients with microprolactinomas and the 24 patients with macroprolactinomas who had persistent abnormalities on MRI. The P values were calculated with the log-rank test. In none of the patients with a recurrence of hyperprolactinemia after cabergoline withdrawal did the tumor reappear or increase in size.

DISCUSSION

Our study showed that, in general, remission of hyperprolactinemia persisted after the withdrawal

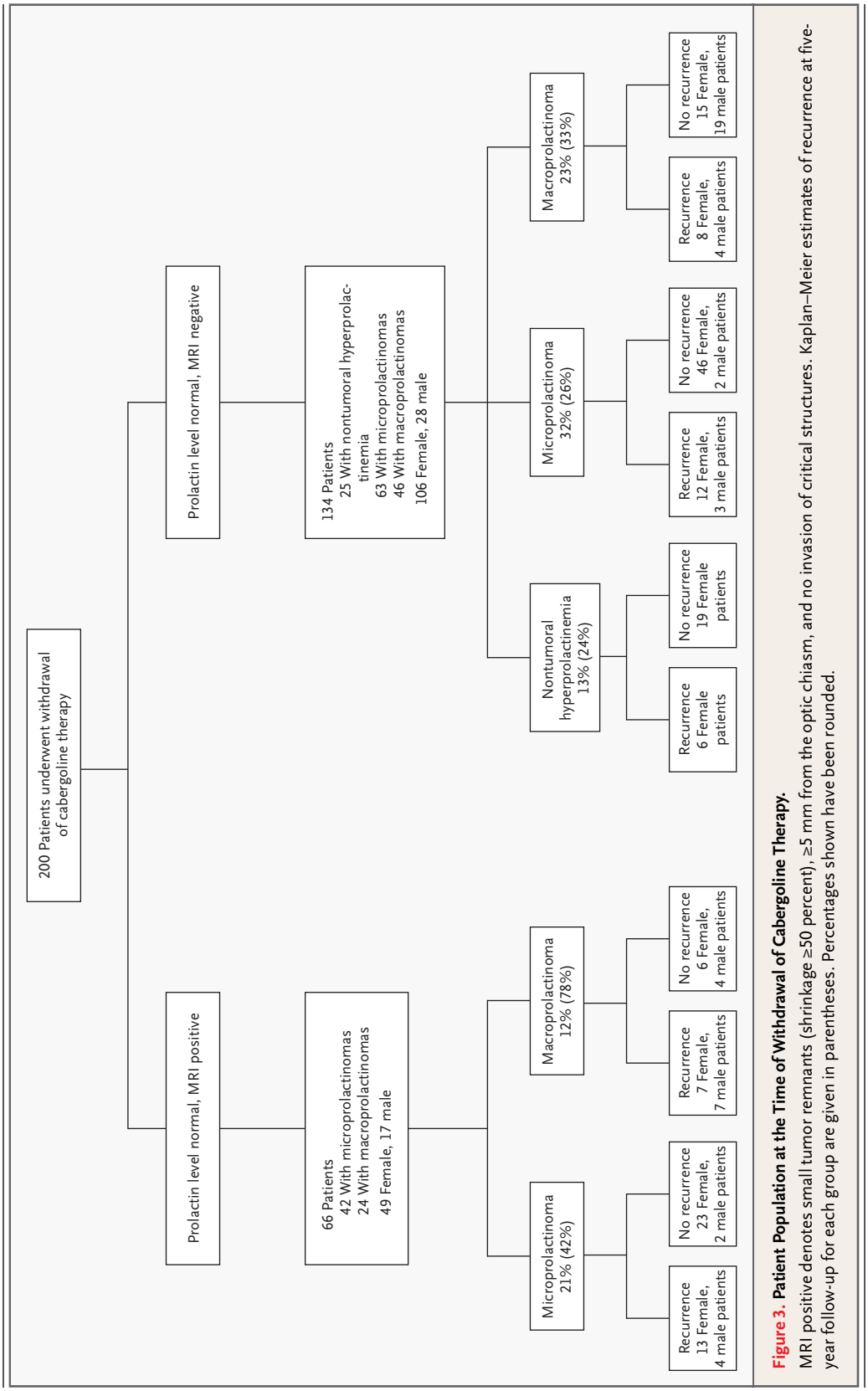

Figure 3. Patient Population at the Time of Withdrawal of Cabergoline Therapy.

MRI positive denotes small tumor remnants (shrinkage ≥50 percent), ≥5 mm from the optic chiasm, and no invasion of critical structures. Kaplan–Meier estimates of recurrence at five-year follow-up for each group are given in parentheses. Percentages shown have been rounded.

of cabergoline, without any evidence of renewed tumor growth. Neither sex nor age was associated with the recurrence of hyperprolactinemia, and the maximal tumor diameter during treatment with cabergoline was the best predictor of the prolactin level at the last follow-up visit after withdrawal, with a hazard rate to predict recurrence of 19 percent.

The efficacy of the primary treatment of both microprolactinoma and macroprolactinoma with dopamine-agonist compounds and, more specifically, with cabergoline, is widely documented.[7-11,22-30] Cabergoline therapy has also been successful in patients whose prolactinomas were resistant to bromocriptine or who could not tolerate bromocriptine,[26,27] with a success rate of over 90 percent in patients with newly diagnosed prolactinomas.[10,23,29] The most important shortcoming of medical treatment has been considered to be its theoretically lifelong requirement.

The results of bromocriptine withdrawal have been reported after a wide range of follow-up periods (8 to 240 months; median, 24). The results have been variable, with normoprolactinemia sustained in 7 to 38 percent of patients.[15-21,31] Notably, an increase in tumor volume with clear reexpansion has been found in approximately 10 percent of cases.[15,17] Renewed growth of the tumor after discontinuation of bromocriptine therapy, however, seems to depend on the duration of treatment before drug withdrawal: the tumors appear to be most susceptible to renewed growth after a course of treatment of less than 12 months.[32-35]

Withdrawal of cabergoline has been reported in only a few studies. One study reported persistent normoprolactinemia in 1 patient of 9 with a macroprolactinoma (11 percent) and 4 patients of 18 with microprolactinomas (22 percent) 12 months after withdrawal[23]; another reported that there was no change in prolactin levels in 24 percent of 25 patients after 3 to 60 months[36] and in 31 percent of 32 patients who were treated for 3 to 24 months 12 months after withdrawal.[22] In an earlier study, we found that normoprolactinemia persisted 12 months after withdrawal in 17 percent of 23 patients with microprolactinomas who were treated with cabergoline for 12 months.[25] An important shortcoming of previous studies was the lack of criteria for timing withdrawal: in those studies cabergoline was apparently withdrawn after varying periods (12 months, on average), without systematic evaluation of the outcome of withdrawal with respect to prolactin suppression and tumor shrinkage.

Because the possibility of inducing long-lasting control of hyperprolactinemia without continuing pharmacologic treatment has profound consequences not only for patients' compliance but also for the costs of treatment, we designed our study to determine the rate of success of cabergoline withdrawal and potentially useful criteria for identifying patients with the highest likelihood of prolactin control after the discontinuation of cabergoline therapy. According to the literature on bromocriptine withdrawal,[15-21,31] achieving normoprolactinemia is the first criterion and a mandatory one. We chose tumor shrinkage as an additional criterion and divided our patients on the basis of the extent of tumor shrinkage into two groups, those whose tumor disappeared and those in whom a 50 percent or greater reduction occurred from base line in a tumor mass that was not near the optic chiasm or invading the cavernous sinuses or other critical cerebral areas. Previous morphologic studies of tumor specimens obtained after long-term treatment with bromocriptine have shown atrophic tumor-cell nests, pyknosis, and cytolysis, as well as karyorrhexis, necrosis, fibrosis, hyalinosis, and inflammatory-cell infiltration, suggesting a cytocidal effect of the drug.[37] We attribute our high rate of stable normoprolactinemia without tumor recurrence, even among patients with macroprolactinomas, to an effective antitumoral effect of cabergoline.

It should also be noted that even though patients whose MRI studies showed no evidence of tumor had a significantly lower rate of recurrence than those with visible tumors on MRI, 59 percent of patients with small, remnant microprolactinomas and 23 percent of those with small, remnant macroprolactinomas had persistent normoprolactinemia after cabergoline withdrawal. This finding suggests that in some of these patients the abnormalities detected on MRI may have been small, nonfunctioning lesions, fibrotic scars, or other nontumoral abnormalities (incidentalomas).

We excluded patients with certain conditions, such as pregnancy,[38,39] previous surgery, and radiotherapy, that are known to facilitate the occurrence of normoprolactinemia after dopamine-agonist withdrawal. Menopause might be considered a factor that influences the reduction of hyperprolactinemia,[40] but the rate of recurrence of hyperprolactinemia was similar among patients who were premenopausal and those who were postmenopausal. Remission of prolactinomas has also been described as part of the natural history of untreated

tumors.[41-43] However, even allowing for the possible role of this natural history in the outcome of microprolactinomas, it seems unlikely that macroprolactinomas would spontaneously regress. In our study, the overall rates of remission at five years as estimated by the Kaplan–Meier method were 76 percent among patients with nontumoral hyperprolactinemia, 67 percent among those with microprolactinomas, and 57 percent among those with macroprolactinomas, rates that are higher than those generally reported in the literature as spontaneous regression.

Our data support the concept of periodic withdrawal of cabergoline therapy, especially in patients with negative MRI studies during treatment. The risk of recurrent hyperprolactinemia with each millimeter increment in the size of the tumor remnant was 19 percent. However, until data from a study with a longer follow-up period are available, close monitoring for recurrent hyperprolactinemia and renewed tumor growth is important, particularly in patients with macroprolactinomas, in whom renewed growth may compromise vision.

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