Intracranial Meningiomas Decrease in Volume on Magnetic Resonance Imaging After Discontinuing Progestin

Eduard H. J. Voormolen, MD, PhD*
Pierre Olivier Champagne, MD*
Elena Roca, MD*
Lorenzo Giammattei, MD*
Thibault Passeri, MD*
Paolo di Russo, MD*
Miguel Marigil Sanchez, MD, PhD*
Anne Laure Bernat, MD*
Isabelle Yoldjian, MD‡
Sylvie Fontanel, MD§
Alain Weill, MD¶
Emmanuel Mandonnet, MD, PhD*
Sébastien Froelich, MD*

*Department of Neurosurgery, Lariboisiere Hospital, University of Paris Diderot, Paris, France; ‡National Agency for the Safety of Medicines and Health Products (ANSM), Paris, France; §Grand Est Regional Health Authority, Nancy, France; ¶Scientific Interest Group–Health Product Epidemiology (ANSM-CNAM EPI-PHARE SIG), National Health Insurance, Department of Public Health Studies, Saint-Denis, France

Correspondence:
Eduard H. J. Voormolen, MD, PhD,
Department of Neurosurgery,
Hôpital Lariboisière,
Assistance Publique—Hôpitaux de Paris,
Université Paris—Diderot,
2 rue Ambroise Pare,
75010 Paris, France.
Email: ehjvoormolen@gmail.com

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BACKGROUND: The behavior of meningiomas under influence of progestin therapy remains unclear.

OBJECTIVE: To investigate the relationship between growth kinetics of intracranial meningiomas and usage of the progestin cyproterone acetate (PCA).

METHODS: This study prospectively followed 108 women with 262 intracranial meningiomas and documented PCA use. A per-meningioma analysis was conducted. Changes in meningioma volumes over time, and meningioma growth velocities, were measured on magnetic resonance imaging (MRI) after stopping PCA treatment.

RESULTS: Mean follow-up time was 30 (standard deviation [SD] 29) mo. Ten (4%) meningiomas were treated surgically at presentation. The other 252 meningiomas were followed after stopping PCA treatment. Overall, followed meningiomas decreased their volumes by 33% on average (SD 28%). A total of 188 (72%) meningiomas decreased, 51 (19%) meningiomas remained stable, and 13 (5%) increased in volume of which 3 (1%) were surgically treated because of radiological progression during follow-up after PCA withdrawal. In total, 239 of 262 (91%) meningiomas regressed or stabilized during follow-up. Subgroup analysis in 7 women with 19 meningiomas with follow-up before and after PCA withdrawal demonstrated that meningioma growth velocity changed statistically significantly ($P = .02$). Meningiomas grew (average velocity of 0.25 mm^3/day) while patients were using PCA and shrank (average velocity of −0.54 mm^3/day) after discontinuation of PCA.

CONCLUSION: Ninety-one percent of intracranial meningiomas in female patients with long-term PCA use decrease or stabilize on MRI after stopping PCA treatment. Meningioma growth kinetics change significantly from growth during PCA usage to shrinkage after PCA withdrawal.

KEY WORDS: Meningioma, Progestin, Volumetric MRI

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The biological relationship between growth of meningiomas and sex hormones is subject of debate.[1,2] A relationship between progesterone and meningioma growth seems probable considering the following findings.

Meningiomas show a female predominance as evidenced by a female-to-male ratio of 2:1. Meningiomas exhibit an acceleration of tumor growth during pregnancy[3-6] and shrinkage after childbirth.[7] Eighty percent of meningiomas express progesterone receptors.[8] These receptors are overexpressed in meningiomas compared to normal meningeal tissue, and the expression of progesterone receptors in meningiomas is higher in women.[8]

A relationship between meningioma growth and exogenous progestins also seems probable. Recently, a nationwide cohort study in France demonstrated that women treated with the progestin cyproterone acetate (PCA) or Androcur®(Bayer Pharmaceuticals, Leverkusen, Germany) exhibited a 7- to 20-fold higher risk to develop a meningioma.[9] PCA is prescribed

ABBREVIATION: PCA, progestin cyproterone acetate

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for hyperandrogenism, contraception, ovarian dysfunction, and several other indications in European countries, including France and the UK.[9-11] Furthermore, several case reports showed regression of meningiomas after stopping PCA.[12-15]

This study investigates meningioma growth kinetics in relation to usage of PCA in a case series of adult women who used PCA for a variety of indications but primarily hyperandrogenism. The goal is to consolidate the hypothesis that meningiomas grow during progestin use and stabilize, or even decrease in size, once progestins are discontinued.

METHODS

Ethics Approval

This study was approved by the local ethics committee of Pôle Neurosciences of Lariboisière Hospital, Paris, France. Written patient consent for inclusion in this study was obtained and recorded.

Inclusion and Exclusion Criteria

From a prospectively collected database of patients referred to the outpatient clinic because of intracranial meningiomas and PCA use, we retrospectively selected a population of patients suitable for analysis in this study.

The following inclusion criteria were formulated. Patients should have the following:

1. Presence of at least 1 intracranial meningioma,
2. Documented PCA usage,
3. Presence of at least 2 sequential brain magnetic resonance imaging (MRI) with 3D T1 gadolinium-enhanced sequences,
4. Presence of at least 1 brain MRI performed after stopping PCA usage.

The exclusion criterion was a history of co-usage of nomegestrol acetate.

Meningioma Characteristics

A per-meningioma analysis was performed. For each meningioma the following characteristics were gathered: laterality, general location, precise location, dates of MRI, and volumes on MRI. Moreover, any occurrence of radiotherapy/radiosurgery was also noted.

Surgery and Radiotherapy

Surgery, indication for surgery, tumor grade, hormone receptors, and radiotherapy/radiosurgery were noted.

Definitions of Meningioma Location

Meningioma location was divided in 5 categories: anterior, middle and posterior cranial fossa, convexity, and midline.

These 5 general locations were subdivided into several specific locations. Anterior cranial fossa included orbital roof, optic nerve sheath, olfactory groove, anterior clinoid, planum, and tuberculum sellae meningiomas. Middle cranial fossa included cavernous sinus, sphenoid wing, spheno-orbital, and genuine middle fossa meningiomas. Posterior cranial fossa consisted of cerebellopontine angle and tentorial meningiomas. Convexity included frontal, parietal, and temporal convexity meningiomas. The midline category consisted of parasagittal and falx meningiomas.

Meningioma Volume

For each meningioma, we calculated volumetric differences between different timepoints during follow-up.

The "percentage volumetric difference post-PCA withdrawal," or $dP_{\text{post PCA}}$, is defined in formula 1:

$$dP_{\text{post PCA}} = \left(dV_{\text{post PCA}} \div V_{\text{stop date}}\right) \times 100\%, \quad (1)$$

where $V_{\text{stop date}}$ is the meningioma volume on the MRI performed closest in time to the PCA withdrawal date, whereas $dV_{\text{post PCA}}$ is the "volumetric difference post-PCA withdrawal" defined in formula 2:

$$dV_{\text{post PCA}} = V_{\text{stop date}} - V_{\text{ffinal date,}} \quad (2)$$

where $V_{\text{final date}}$ is the meningioma volume on the MRI made at last follow-up.

Moreover, the "percentage volumetric difference post-PCA withdrawal" was used to define a categorical variable to convey in a more intuitive manner how a meningioma responded volumetrically to stopping PCA. This variable is referred to as "volumetric response." Volumetric response has 3 possible values, namely "decrease," "stable," or "increase," which are defined below.

Volumetric response:

- Decrease: $dP_{\text{post PCA}} < (-E_{\text{interrater}})$,
- Stable: $(E_{\text{interrater}}) > dP_{\text{post PCA}} < (-E_{\text{interrater}})$,
- Increase: $dP_{\text{post PCA}} > (E_{\text{interrater}})$,

where $E_{\text{interrater}}$ is the mean percentage of interrater error plus 2 standard deviations (SDs). Each meningioma was categorized accordingly.

Meningioma Velocity

Furthermore, meningioma velocities were calculated. The "meningioma velocity post-PCA withdrawal," or $Mv_{\text{post PCA}}$, was calculated as defined in formula 3:

$$Mv_{\text{post PCA}} = dV_{\text{post PCA}} \div dT_{\text{post PCA,}} \quad (3)$$

where $dT_{post\ PCA}$ is defined as the time difference (in days) between the date of the MRI performed closest in time to the PCA withdrawal date, and the date of the MRI at last follow-up.

Measurement of Volumes

Volumetric measurements were performed with PACS viewer software (Carestream version 12.1.6.0116; Carestream Health Inc, Rochester, New York). Outlining was performed manually slice by slice by 2 board certified neurosurgeons on the axial 3D T1 gadolinium-enhanced MRI sequences. The meningioma volume used in all analyses was the average of the volumes of both raters.

Subgroup Selection

A specific subgroup was selected to answer the question if there is a difference in growth velocity during usage and after withdrawal of PCA in the same patients. The additional subgroup selection criteria were:

- Presence of at least 2 brain MRI acquired during PCA usage,
- Presence of at least 1 brain MRI after stopping PCA.

TABLE 1. Baseline Characteristics of Study Population

		Mean	SD	Range
Age	(years)	50.1	8.8	31-72
BMI	(index)	26.1	6.2	18-35
Annual PCA dose	(mg)	12 690	4272	4562.5-27 375
Years of PCA usage	(years)	17.4	6.3	3-30
Initial KPS	(points)	99.3	2.9	80-100
No. of meningiomas	(#)	2.4	2.2	1-13
Meningioma volume at presentation	(mm^3)	5648	17 691	9-134 100
		#	%	
Meningiomatosis		31	29	
Indication for PCA	Hyperandrogenism	22	20.2	
	Acne	18	16.5	
	Hair loss	17	15.6	
	Hirsutism	16	14.7	
	Contraception	13	11.9	
	PCOS	10	9.2	
	Endometriosis	3	2.8	
	Dysmenorrhea	3	2.8	
	Breast cysts	3	2.8	
	Menopause	3	2.8	
	Bilateral ovariectomy	1	0.9	
Presenting symptoms	Asymptomatic	68	63.0	
	Headache	19	17.6	
	Visual symptoms	13	12.0	
	Epilepsy	2	1.9	
	Sensory deficit	2	1.9	
	Cognitive symptoms	2	1.9	
	Cranial nerve deficit	1	0.9	

BMI = body mass index. KPS = Karnofsky Performance Score. SD = standard deviation. PCA = cyproterone acetate. PCOS = polycystic ovarian syndrome.
Baseline characteristics of our study population.

Statistical Analysis

Linear regression analyses were performed with IBM SPSS Statistics (version 25; Armonk, New York). Unadjusted r^2 and R^2 are reported. For the subgroup analysis, a paired 2-tailed t-test was performed to compare the "meningioma velocity during PCA treatment" with "meningioma velocity post-PCA withdrawal." A *P*-value of $<.05$ was considered to indicate a significant difference.

RESULTS

Participants

Our database contained 132 patients. Within this database, 112 patients met the inclusion criteria. 20 patients were not included because they did not have 2 sequential MRI with T1-weighted gadolinium enhanced sequences at the time of analysis. Four patients were excluded because of nomegestrol acetate co-usage. Finally, the data of 108 women with a total of 262 meningiomas were analyzed. The mean follow-up period was 30 ± 29 mo (median 18 mo).

Baseline Characteristics

Results for baseline measures are given in Table 1. All patients were female. The mean age of participants was 50 (SD 9) yr, and they had a mean body mass index (BMI) of 26 (SD 6). The women were treated with a daily dosage of PCA ranging between 25 and 75 mg, corresponding to a mean yearly PCA dosage of 12 690 (SD 4272) mg, with a mean period of usage of 18 (SD 6.4) yr. The most common indications for PCA prescription were hyperandrogenism (20.2%) and related symptoms such as acne (16.5%) or hair loss (15.6%). Approximately 11.9% of women used PCA for contraception. However, the choice for PCA was also partly based on additional signs of hyperandrogenism in this patient category. Patients had on average 2.4 (SD 2.2) meningiomas, and 29% met criteria of meningiomatosis (defined as 3 or more meningioma). Most patients were asymptomatic (63%) or had headaches (18%) as initial symptoms.

Meningioma Locations

Results for meningioma locations are given in Table 2. The most common general location for meningiomas was convexity

TABLE 2. Location of Meningiomas

General location	#	%	Precise location	#	%
Convexity	94	36	Frontal convexity	58	22
Anterior cranial fossa	86	33	Frontobasal	41	16
Middle cranial fossa	60	23	Sphenoid wing	36	14
Midline	14	5	Temporal convexity	21	8
Posterior cranial fossa	8	3	Olfactory groove	19	7
			Parietal convexity	15	6
			Tuberculum sellae	14	5
			Cavernous sinus	10	4
			Parasagittal	9	3
			Anterior clinoid	8	3
			Spheno-orbital	7	3
			Middle fossa	7	3
			Tentorium	6	2
			Falx	5	2
			Optic sheet	4	2
			Cerebellopontine angle	2	1

This table depicts the frequency of meningiomas at different anatomic locations as encountered in our study population.

(36%) and anterior cranial fossa (33%), and the most common specific location was frontal convexity (22%).

Surgery and Radiotherapy

Ten (3.81%) meningiomas in 9 patients had surgery within 3 mo after presentation, and within 3 mo of stopping PCA, because of progressive symptoms. Three (1.2%) meningiomas had surgery because of radiological progression despite cessation of PCA. Twelve were meningothelial WHO grade I meningiomas, and 1 was a transitional type WHO I meningioma. All had an expression of progesterone receptors. Ki-67 labeling index ranged between 1% and 4%.

Three (1.15%) meningiomas were irradiated in 2 patients. The first patient had a cavernous sinus meningioma, first irradiated with photon during PCA treatment and later operated on shortly after presentation. The other patient had 2 meningiomas (optic sheath and temporal convexity) that received proton irradiation 5 yr after withdrawal of PCA because of a progressive visual loss.

Interrater Correspondence

The 2 raters had a mean relative interrater difference between volume measurements of 2.1% (SD 3.4). Accordingly, the value for $E_{\text{interrater}}$ (see Methods section) to determine volumetric response was calculated at 9%.

Meningioma Volumes and Velocity

Volume analysis was conducted for 252 meningiomas. Ten meningiomas (3.8%), operated on at presentation, were excluded. There was an overall decrease in volume of −1628 (SD 6924) mm^3, or −33.2 (SD 34.4)%, and a "shrinkage" or negative growth velocity of −5.8 (SD 28.3) mm^3/day, which amounts to −2.1 cm^3/yr, after stopping PCA treatment. Figure shows results of the volume analysis.

In terms of volumetric response (see Methods section for definition), 188 (71.76%) meningiomas decreased, 51 (19.46%) meningiomas remained stable, and 13 (4.96%) increased after withdrawal of PCA.

Linear regression modeling (Table 3) was performed to predict meningioma growth velocity after stopping PCA treatment from the following parameters: meningiomatosis, amount of meningiomas, years of usage, cumulative dose, BMI, age, general location, precise location, and meningioma start volume.

Univariate modeling was used to select variables for a multivariate model. The following variables were found to significantly add ($P < .05$) to the prediction of meningioma growth velocity during univariate modeling: amount of meningiomas ($r^2 = 0.17$, $P = .04$), presence of meningiomatosis ($r^2 = 0.03$, $P = .01$), precise location ($r^2 = 0.02$, $P = .02$), and meningioma start volume ($r^2 = 0.2$, $P = .00$).

During multivariate modeling, a significant regression equation was found $F(4, 254) = 17.65$, $P = .000$, with an R^2 of 0.22. Only meningioma start volume ($t = -7.39$, $P = .00$) remained as a statistically significantly ($P < .05$) predictor. See Table 3 for additional details regarding the regression models.

Subgroup Results

Furthermore, 7 patients with a total of 19 meningiomas were included in the subgroup analysis to answer the question if there is a difference in growth velocity during usage and after PCA cessation.

The mean age of the subgroup was 49 (SD 7) yr. The mean BMI was 26 (SD 6). The subgroup was treated with a daily dosage of PCA of 25 or 50 mg, corresponding to a mean yearly PCA dosage of 9033 (SD 248) mg, with a mean usage period of 18 (SD 4) yr. Patients had on average of 2.7 (SD 2.0) meningiomas, and 38% had meningiomatosis. Approximately 83% were asymptomatic or had headaches (17%) as presenting symptoms.

During PCA use, the overall meningioma growth was 0.25 (SD 0.45) mm^3/day, whereas after treatment withdrawal, there was an overall meningioma shrinkage of −0.54 (SD 1.26) mm^3/day. This growth velocity change was statistically significant ($P = .02$ in 2-tailed paired sample t-test).

DISCUSSION

The presented results suggest that usage of exogenous progestin influences growth kinetics of intracranial meningioma in adult women. Regression modeling demonstrated that meningioma start volume significantly predicted meningioma growth velocity after discontinuation of PCA. This seems logical because a larger meningioma volume entails relatively larger growth or shrinkage. During multivariate analysis, this effect overwhelmed the effect of the amount of meningiomas, presence of meningiomatosis, and

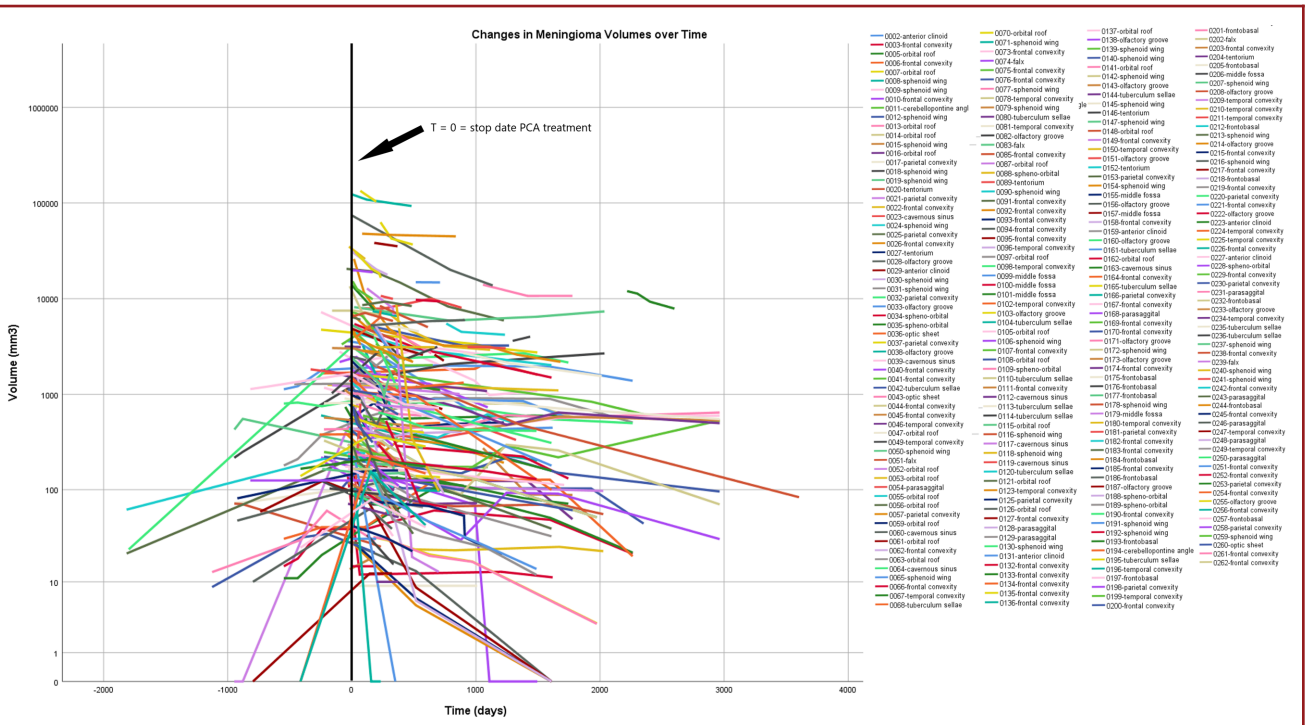

FIGURE. *This figure shows the change in volume over time of 252 meningiomas in our series. Time = 0 is the day patients discontinued usage of cyproterone acetate.*

precise meningioma location, which were significant in univariate modeling.

Comparison to Previous Studies

The natural history of "incidental" meningiomas without documented exposure to progestins has been studied extensively.[16-21] About 70% to 75% of these meningiomas exhibit growth over time, and 25% to 30% do not grow significantly.[18,19] Different patterns of growth (eg, linear, exponential, or sigmoidal) have been identified.[17,21] Meningioma shrinkage has been described but is a rare phenomenon.[18]

In comparison, the results presented in this series of PCA-associated meningiomas are strikingly different from previous reports about "incidental" meningiomas. For example, Oya et al [22] reported that in a study of 244 patients with 277 meningiomas, 44% of meningiomas progressed over a follow-up time of 3 to 4 yr, and regression of meningiomas did not occur. Conversely, after discontinuation of PCA treatment, the meningiomas in this series progressed in 5% and regressed in 71%. Of the 13 meningiomas (5%) that progressed, 2 were single meningiomas. These 2 cases could represent incidental meningiomas without sensitivity to exogenous progestin. The other 11 showed growth, whereas other meningiomas in the same patient remained stable or regressed.

Furthermore, Nakamura et al[20,23] published 2 reports demonstrating that meningiomas have positive growth velocities ranging between 0.796 and 1.51 cm^3/yr. Contrarily, the meningiomas in our population had a mean negative velocity (shrinkage) of −2.1 cm^3/yr after cessation of PCA. We presume these differences in meningioma growth kinetics are due to progestin effects.

Moreover, we believe that the high incidence of 29% meningiomatosis as seen in our population is related to PCA. A similar trend was also shown in a recent publication from Peyre et al.[24] It suggests that progestin induces the initiation of tumors from multiple meningeal cells.

Biological Mechanism

The underlying mechanism how PCA influences the behavior of meningiomas remains unknown. Progesterone has been shown to have a direct positive effect on the proliferation of meningioma cells,[25,26] but can also lead to increased angiogenesis[27] with related alterations in hemodynamics.[6] It might be that the PIK3CA/AKT1 pathways determine the PCA-driven mechanism, as it was recently shown that 33% of PCA-induced meningioma exhibit mutations in these signaling pathways, vs only 11% in incidental meningioma.[28]

Limitations

A limitation of this study is an interrater error of 2% in the meningioma volume measurements because it might be that subtle changes were missed because of averaging between 2 raters with differing measurements. Moreover, the accuracy of the

TABLE 3. Linear Regression Models

Predictor	Models	USC B	SE	SC beta	t value	Sig.	95% CI for B Low.	95% CI for B Upp.	R^2	Adj. R^2
Meningiomatosis	Univariate	9.99	3.61	0.17	2.77	0.01*	2.88	17.09	0.03	0.03
	Multivariate	5.09	4.51	0.09	1.13	0.26	−3.79	13.97	0.22	0.21
No. of meningiomas	Univariate	1.11	0.53	0.13	2.08	0.04*	0.06	2.15	0.02	0.01
	Multivariate	0.01	0.66	0.00	0.01	0.99	−1.29	1.31	0.22	0.21
Years of PCA usage	Univariate	−0.09	0.30	−0.02	−0.30	0.77	−0.67	0.49	0.00	−0.00
	Multivariate	–	–	–	–	–	–	–	–	–
Cumulative PCA dose	Univariate	−0.00	0.00	−0.04	−0.57	0.57	0.00	0.00	0.00	−0.00
	Multivariate	–	–	–	–	–	–	–	–	–
Body mass index	Univariate	0.25	0.15	0.19	1.68	0.1	−0.05	−0.42	0.04	0.02
	Multivariate	–	–	–	–	–	–	–	–	–
General location	Univariate	−0.36	1.61	−0.01	−0.22	0.83	−3.53	2.82	0.00	−0.00
	Multivariate	–	—	–	–	–	–	–	–	–
Precise location	Univariate	−0.98	0.40	−0.15	−2.44	0.02*	−1.77	−0.19	0.02	0.02
	Multivariate	−0.73	0.37	−0.11	−1.99	0.05	−1.45	−0.00	0.22	0.21
Age	Univariate	−0.02	0.23	−0.00	−0.07	0.95	−0.46	0.43	0.00	−0.00
	Multivariate	–	–	–	–	–	–	–	–	–
Start volume	Univariate	−0.00	0.00	−0.45	−7.92	0.00*	−0.00	−0.00	0.20	0.20
	Multivariate	−0.00	0.00	−0.42	−7.39	0.00*	−0.00	−0.00	0.22	0.21

USC B: unstandardized regression coefficient; SC Beta: standardized coefficient; R^2: squared multiple correlation coefficient; SE: standard errors of the regression coefficients; Sig: 2-sided observed significance levels (p) for the t statistics. CI: confidence interval; PCA, progestin cyproterone acetate.

*Significant *P* values.

The predictors (independent variables) meningiomatosis, amount of meningiomas, years of PCA usage, cumulative PCA dose, body mass index, general location, precise location, age, and meningioma start volume were used to predict meningioma growth velocity after discontinuation of PCA (dependent variable).

volumetric response categorization is similarly limited because of the interrater error, which causes subtle growth or subtle shrinkage within this error margin to be underreported. Because this study was designed as a case series, we compared our results to previous data from the literature about meningioma growth instead of an internal control group. Follow-up time was 3 yr on average, which means it is unclear whether the reported effects on meningioma volumes are sustainable over time. It is worth noting that secondary progression of a meningioma that initially regressed was not observed in this series.

Implications

According to our results, current or previous use of progestin therapy (in particular PCA) should be systematically sought in the history of a patient with meningiomas. In the event of prolonged exposure to PCA for multiple years and in the absence of symptoms requiring urgent surgery, discontinuation should be the first option to consider. Given the frequent spontaneous stabilization and regression of meningiomas after discontinuation of treatment, surgery or radiotherapy only seems indicated in the event of progression despite discontinuation of PCA.

In this study, it was medically possible to cease PCA treatment in all included patients. However, the consequences of cessation are important to consider, eg, the resulting recurrence of hyperandrogenic symptoms or dysmenorrhea. Caution should also be exercised regarding therapeutic alternatives based on progestins, such as chlormadinone acetate or nomegestrol acetate, because some of these treatments might also promote growth of meningiomas.[14,24,29,30]

Further Research

More data are needed on the dose effect of PCA on meningioma kinetics in order to evaluate whether PCA could be pursued in a very low dosage in case of severe symptoms and/or psychological burden.

CONCLUSION

The behavior of intracranial meningiomas in adult female patients with documented long-term PCA use was investigated. The majority of these meningiomas decrease in volume (71%) or stabilize (19%) after withdrawal of PCA treatment. Meningioma growth kinetics change significantly from growth under PCA treatment to shrinkage after PCA withdrawal. Therefore, PCA seems to influence meningioma growth kinetics in this population. In the absence of symptoms requiring urgent surgery, PCA discontinuation could be considered as the primary treatment option for these patients.

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REFERENCES

1. Benson VS, Pirie K, Green J, Casabonne D, Lifestyle factors and primary glioma and meningioma tumours in the Million Women Study cohort. *Br J Cancer*. 2008;99(1):185-190.
2. Wigertz A, Lönn S, Mathiesen T, Ahlbom A, Hall P, Feychting M. Risk of brain tumors associated with exposure to exogenous female sex hormones. *Am J Epidemiol*. 2006;164(7):629-636.
3. Ismail K, Coakham HB, Walters FJ. Intracranial meningioma with progesterone positive receptors presenting in late pregnancy. *Eur J Anaesthesiol*. 1998;15(1):106-109.
4. Saitoh Y, Oku Y, Izumoto S, Go J. Rapid growth of a meningioma during pregnancy: relationship with estrogen and progesterone receptors–case report. *Neurol Med Chir*. 1989;29(5):440-443.
5. Bickerstaff ER, Small JM, Guest IA. The relapsing course of certain meningiomas in relation to pregnancy and menstruation. *J Neurol Neurosurg Psychiatry*. 1958;21(2):89-91.
6. Lusis EA, Scheithauer BW, Yachnis AT, et al. Meningiomas in pregnancy: a clinicopathologic study of 17 cases. *Neurosurgery*. 2012;71(5):951-961.
7. Smith JS, Quiñones-Hinojosa A, Harmon-Smith M, Bollen AW, McDermott MW. Sex steroid and growth factor profile of a meningioma associated with pregnancy. *Can J Neurol Sci*. 2005;32(1):122-127.
8. Hsu DW, Efird JT, Hedley-Whyte ET. Progesterone and estrogen receptors in meningiomas: prognostic considerations. *J Neurosurg*. 1997;86(1):113-120.
9. Weill A, Nguyen P, Labidi M, et al. Use of high dose cyproterone acetate and risk of intracranial meningioma in women: cohort study. *BMJ*. 2021;372:n37.
10. Ruan X, Kubba A, Aguilar A, Mueck AO. Use of cyproterone acetate/ethinylestradiol in polycystic ovary syndrome: rationale and practical aspects. *Eur J Contracept Reprod Health Care*. 2017;22(3):183-190.
11. Stegeman BH, de Bastos M, Rosendaal FR, et al. Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis. *BMJ*. 2013;347:f5298-f5298.
12. Bernat AL, Oyama K, Hamdi S, et al. Growth stabilization and regression of meningiomas after discontinuation of cyproterone acetate: a case series of 12 patients. *Acta Neurochir*. 2015;157(10):1741-1746.
13. Cebula H, Pham TQ, Boyer P, Froelich S. Regression of meningiomas after discontinuation of cyproterone acetate in a transsexual patient. *Acta Neurochir*. 2010;152(11):1955-1956.
14. Champagne P-O, Passeri T, Froelich S. Combined hormonal influence of cyproterone acetate and nomegestrol acetate on meningioma: a case report. *Acta Neurochir*. 2019;161(3):589-592.
15. Gonçalves AMG, Page P, Domigo V, Oppenheim C. Abrupt regression of a meningioma after discontinuation of cyproterone treatment. *AJNR Am J Neuroradiol*. 2010;31(8):1504-1505.
16. Sughrue ME, Rutkowski MJ, Aranda D, Barani IJ, McDermott MW, Parsa AT. Treatment decision making based on the published natural history and growth rate of small meningiomas. *J Neurosurg*. 2010;113(5):1036-1042.
17. Hashiba T, Hashimoto N, Izumoto S, et al. Serial volumetric assessment of the natural history and growth pattern of incidentally discovered meningiomas. *J Neurosurg*. 2009;110(4):675-684.
18. Behbahani M, Skeie GO, Eide GE, Hausken A, Lund-Johansen M, Skeie BS. A prospective study of the natural history of incidental meningioma-Hold your horses! *Neurooncol Pract*. 2019;6(6):438-450.
19. Jadid KD, Feychting M, Höijer J, Hylin S, Kihlström L, Mathiesen T. Long-term follow-up of incidentally discovered meningiomas. *Acta Neurochir*. 2015;157(2):225-230; discussion 230.
20. Nakamura M, Roser F, Michel J, Jacobs C, Samii M. The natural history of incidental meningiomas. *Neurosurgery*. 2003;53(1):62-71; discussion 70-71.
21. Nakasu S, Nakasu Y, Fukami T, Jito J, Nozaki K. Growth curve analysis of asymptomatic and symptomatic meningiomas. *J Neurooncol*. 2011;102(2):303-310.
22. Oya S, Kim S-H, Sade B, Lee JH. The natural history of intracranial meningiomas. *J Neurosurg*. 2011;114(5):1250-1256.
23. Nakamura M, Roser F, Michel J, Jacobs C, Samii M. Volumetric analysis of the growth rate of incompletely resected intracranial meningiomas. *Zentralbl Neurochir*. 2005;66(1):17-23.
24. Peyre M, Gaillard S, de Marcellus C, et al. Progestin-associated shift of meningioma mutational landscape. *Ann Oncol*. 2018;29(3):681-686.
25. Blankenstein MA, Verheijen FM, Jacobs JM, Donker TH, van Duijnhoven MW, Thijssen JH. Occurrence, regulation, and significance of progesterone receptors in human meningioma. *Steroids*. 2000;65(10-11):795-800.
26. Koper JW, Foekens JA, Braakman R, Lamberts SW. Effects of progesterone on the response to epidermal growth factor and other growth factors in cultured human meningioma cells. *Cancer Res*. 1990;50(9):2604-2607.
27. Carroll RS, Zhang J, Dashner K, Black PM. Progesterone and glucocorticoid receptor activation in meningiomas. *Neurosurgery*. 1995;37(1):92-97.
28. Portet S, Naoufal R, Tachon G, et al. Histomolecular characterization of intracranial meningiomas developed in patients exposed to high-dose cyproterone acetate: an antiandrogen treatment. *Neuro Oncol Adv*. 2019;20(1):1-12.
29. Passeri T, Champagne P-O, Bernat A-L, et al. Spontaneous regression of meningiomas after interruption of nomegestrol acetate: a series of three patients. *Acta Neurochir*. 2019;161(4):761-765.
30. Shimizu J, Matsumoto M, Yamazaki E, Yasue M. Spontaneous regression of an asymptomatic meningioma associated with discontinuation of progesterone agonist administration. *Neurol Med Chir*. 2008;48(5):227-230.

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COMMENT

This is an important paper. Although the use of cyproterone acetate (PCA) is limited in North America, it is used in many countries around the world. The authors identified 108 women with 262 meningiomas who at the time of diagnosis were being treated with PCA. Following the cessation of PCA the study participants were monitored with serial MRIs. An astounding 72% of tumors decreased and a further 19% remained stable in size, thus completely altering the natural history of these meningiomas. I concur entirely with the authors' recommendation that in the absence of symptoms requiring urgent surgery, PCA discontinuation should be the primary treatment option for these patients. Although not specifically addressed by the authors it would seem intuitive that this recommendation be extended to all women with a history of prolonged exposure to any exogenous progestins.

Franco DeMonte
Houston, Texas, USA