Nomegestrol Acetate or Chlormadinone Acetate Progestative Treatment in Women: Meningioma Behavior at Treatment Discontinuation

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Abstract

Background: Associations between progestins and meningiomas is now well established. While the link between cyproterone acetate (CA) and meningioma was thoroughly studied, there is far less available data regarding the link between chlormadinone acetate (CHA) or norgestrel acetate (NA) and risk of intracranial meningioma

Methods: We are presenting a series of 28 patients diagnosed with single or multiple meningiomas while treated with CHA-NA, in which the clinical and radiological course were analyzed after treatment discontinuation.

Results: 28 women, with a mean age of 56 years old, were diagnosed with one or multiple meningioma while being treated with either CHA or NA. After stopping treatment, 89.3% showed either tumor shrinkage or tumor stabilization on follow-up MRIs. Multiple meningiomas were more likely observed in patients with long periods of treatment (>10 years, p 0.03) and seem to have a better clinical course (p 0.01). Most of the lesions were located on the skull base (55.4%). Four patients with multiple meningiomas showed discordant tumors evolution, with some tumors growing while others were decreasing. Most of the growing meningiomas were either convexity or midline lesions and more posteriorly located.

Conclusion: Our study demonstrated a significant percentage of tumor diminution or stabilization after NA and CHA discontinuation. Therefore, treatment discontinuation with close monitoring should be the first measure taken if urgent surgery is not indicated. However, our results seem to be less encouraging than previously described in patients treated by CA, with more patients showing tumor growth despite treatment discontinuation. Further studies are needed to differentiate the effect of the different progestins treatment on meningiomas.

Introduction

Meningioma are the most frequent type of CNS tumors, representing over 30% of primary brain tumors in the population over 35 years of age, with a peak at 65 years [1]. The incidence of meningiomas is more than 2 times higher in the female population. Most meningiomas are benign, with over 80% grade I lesions according to the World Health Organization (WHO) classification and they originate in the arachnoid cells, that naturally express progesterone receptors[2]. Associations between hormones and meningiomas have been studied and are well established over time, with arguments such as: higher incidence in women, tumor growth during pregnancy and regression following child birth, an association between meningiomas and uterine fibroma, endometriosis or breast neoplasia, expression of PR and ER in meningiomas[3–7]. The expression of progesterone receptors in meningiomas has also led to the disappointing testing of antiprogesterone agents, such as mifepristone, that have shown a limited effect on unresectable meningiomas[8, 9].

A strong association between cyproterone acetate (CA), a progesterone derivate and meningioma was first reported in 2008 by Froelich et al[10], in a series of 9 patients with tumor regression after CA discontinuation. Since then, multiple similar reports have been published, and a clear relationship between meningioma and CA is now well established [11–15]. A recent study, based on the French national SNDS database, showed that women who initiated high dose CA treatment had a sevenfold increased risk of surgically treated meningioma with a strong dose-effect. It also confirmed the rapid regression of the risk after CA discontinuation. Since then, measures have been taken by the public health authority in France and in Europe[16–18]. These results concerning the relationship between meningiomas and CA led to an examination of the links between meningiomas and other treatments such as norgestrel acetate or megestrol acetate[19, 20].

Chlormadinone acetate and norgestrel acetate are synthetic progestins, prescribed for progesterone deficiency in premenopausal women (premenstrual syndrome, irregular menstrual cycle, mastodynia), functional uterine bleedings, menorrhagia due to uterine fibromas, endometriosis, dysmenorrhea and contraception (in association with an estrogen)[21, 22].

We have analyzed a series of 28 patients from two neurosurgical centers, presenting with meningioma, diagnosed in the context of treatment with either chlormadinone acetate (CHA) or norgestrel acetate (NA).

Patients And Methods

Since an association between meningioma and progestins was reported, patients presenting with meningiomas in the neurosurgery departments of Lariboisière Hospital in Paris and La Timone Hospital in Marseille were questioned about the use of progestins.

The current study is a retrospective analysis of the clinical and radiological data of 28 patients (17 from Lariboisière Hospital, Paris and 11 from La Timone Hospital, Marseille) diagnosed with one or multiple meningiomas, while treated with either CHA or NA. Treatments were stopped at the time of diagnosis, and all patients were followed clinically and by serial MRIs, with an average of 4.2 months between the end of treatment and first follow-up radiological examination (range from 2 to 6 months).

Patients presenting with severe symptoms at the time of diagnosis, requiring rapid surgery were not included in the study.

Tumor volume measurements were performed by two neurosurgeons on each MRI (MRI at the time diagnosis and the last MRI), using the Carestream® software, by manually contouring each meningioma on each slice. The contouring was then optimized with the 'repulsor' tool. Once the region of interest (ROI) was selected, the volume was automatically calculated with the segmentation function.

Volumetric assessment was based on the total tumor volume for each patient, by calculating the sum of the volumes of all lesions found in multiple meningiomas.

Statistical methods

Data management and analysis was performed with IMBs SPSS (SPSS Statistics 24) and the tests used to compare data were Fisher exact test or chi-square test and Fisher correlation coefficient. The p value considered as significant was < 0.05.

Results

Our study includes 28 female patients, with a mean age of 56 years at the time of diagnosis (range: 37 to 74). 18 patients were treated with NA, 9 had CHA and one patient was treated by NA for 10 years and switched to CHA for another 9 years. The duration of hormonal treatment varied between 1 and 30 years (mean: 13.5 years). Patient's characteristics are summarized in Table 1. Multiple meningiomas (2 or more tumors) were seen in 13 patients, with a maximum of 12 meningiomas in one patient and a total of 65 meningiomas analyzed. Tumor location showed a predisposition for the skull base (36/65 were skull base tumors with only 2 meningiomas located on the posterior skull base), followed by the convexity (23/65) and midline (parasagittal or falx cerebri: 6/65).

Table 1
Patient characteristics

Patient no	Age	Type of hormone	Duration of treatment (years)	Signes and symptoms	Number of meningiomas	Localisation	Clinical outcome	Initial volume (cc)	Final volume (cc)	Volume evolution
1	45	NA	12	Exophthalmia	1	ACF	I	7.5	3.9	R
2	49	NA	17	AS	2	CONV x2	AS	13.8	16.9	G
3	60	NA	10	Palpebral ptosis and 5th nerve neuralgia	1	MCF	I	10.6	9.6	S
4	39	NA then CHA	10 then 9 (total 19)	AS	2	MCF, CONV	AS	5.1	2.8	R
5	45	NA	16	Exophthalmia	1	MCF	I	6.2	3.9	R
6	67	NA	20	Visual impairment	3	ACF x2 MCF	I	11.6	6.2	R
7	37	NA	10	AS	12	MCF x3 CONV x6 MID x3	AS	54.1	33.9	R
8	56	CHA	8	Epilepsy	1	CONV	AS	2.2	2.4	S
9	59	CHA	18	Hard subcutaneous lump	3	CONV ACF PCF	No change	61.2	53.3	R
10	62	CHA	10	AS	2	MCF CONV	AS	8.1	6.8	R
11	64	NA	30	AS	1	ACF	AS	11.1	9.6	R
12	48	NA	8	H/A	1	MCF	AS	1.7	0.6	R
13	45	CHA	15	AS	6	MCF CONV x4 MID	AS	3.5	3.3	S
14	50	NA	9	Visual impairment	1	MCF	I	2.8	1.7	R
15	71	CHA	10	AS	4	ACF MCF CONV x2	AS	3.6	1.5	R
16	64	CHA	16	H/A	1	CONV	No change	7.9	8.1	S
17	49	NA	6	AS	1	CONV	AS	0.4	0.4	R
18	70	NA	20	AS	2	MCF MID	AS	3.8	2.7	R
19	71	NA	20	AS	1	ACF	AS	3.3	3.1	S
20	66	NA	1	AS	1	MID	AS	9.6	9.4	S
21	70	CHA	20	AS	3	ACF x2 CONV	AS	10.1	9.8	S
22	58	CHA	15	Visual impairment	1	MCF	I	2.2	2.3	S
23	54	NA	7	AS	5	ACF x2 PCF CONV x2	AS	17	24.6	G
24	38	CHA	5	Vth nerve neuralgia	1	MCF	AS	6.2	6.5	S

AS – asymptomatic, H/A – headache, ACF – anterior cranial fossa, MCF – middle cranial fossa, PCF – posterior cranial fossa, CONV – convexity, MID – midline, I – improvement, W – sworsening, R – regression, S – stable, G – growth NA – nomegestrol acetate, CHA – chlormadinone acetate

Patient no	Age	Type of hormone	Duration of treatment (years)	Signes and symptoms	Number of meningiomas	Localisation	Clinical outcome	Initial volume (cc)	Final volume (cc)	Volume evolution
25	74	NA	20	AS	3	ACF x2 MCF	AS	3.1	3.5	G
26	56	NA	8	Vth nerve neuralgia	1	MCF	I	0.7	0.3	R
27	58	NA	20	AS	3	ACF x2 CONV	AS	57.1	51.4	S
28	47	NA	9	Vth nerve neuralgia	1	MCF	W	11.9	12.5	S
AS – asymptomatic, H/A – headache, ACF – anterior cranial fossa, MCF – middle cranial fossa, PCF – posterior cranial fossa, CONV – convexity, MID – midline, I – improvement, W – sworsening, R – regression, S – stable, G – growth NA – nomegestrol acetate, CHA – chlormadinone acetate										

Mean duration of progestin treatment in patients with a meningiomatosis was 16 years versus 11.5 years for single meningiomas, indicating that multiple meningiomas are more likely to be found after prolonged use of CHA and NA (p value 0.03). 14 patients were symptomatic (50%), most of them presenting with either visual symptoms (4 patients) or other cranial nerve deficit (4 patients). In the symptomatic group, 11 patients had a single meningioma, suggesting a better clinical course in case of multiple meningiomas (p value 0.01).

After progestin discontinuation, 1 patient among the symptomatic group worsened after 4 months and was operated, 2 remained stable while the other 11 patients (85%) either improved or became asymptomatic. None of the asymptomatic patients at the time of diagnosis became symptomatic during the follow-up period.

The mean follow-up period was 29.4 months (6 to 114 months).

The histological analysis of the resected lesion showed a grade I meningothelial meningioma with a strong positive staining for progesterone receptor by immunochemistry.

An increase in total volume of > 10% was considered as tumor growth. A decrease in total volume of > 10% was considered as tumor regression. In between, the tumor volume was considered stable. In our series, total volume regression was documented in 50% of cases (14 patients), while 10.7% (3 patients) had an increase in volume. 39.3% (11 patients) were considered stable. No association between the number of meningioma or tumor location and tumor volume evolution was established. The evolution of the 65 meningiomas according to their localization is presented in Table 2. Picture 1 illustrates an example of radiological evolution on diagnostic and follow-up MRIs.

Table 2
Tumor localization and evolution on follow-up MRIs

Tumor localization		Regression (n) (p)		Stable (n) (p)		Growth (n) (p)		Total (n) (p)	
Skull base (23/65; 35.4%)	ACF	11	16.9%	3	4.6%	2	3.1%	16	24.6%
	MCF	12	18.5%	5	7.7%	0	0%	17	26.2%
	PCF	1	1.5%	1	1.5%	1	1.5%	3	4.6%
Non skull base (29/65; 64.6)	CONV	13	20%	7	10.8%	3	4.6%	23	35.4%
	MIDL	4	6.1%	0	0%	2	3.1%	6	9.2%
Total		41	63%	16	24.6%	8	12.3%	65	100

In 4 patients with multiple lesions, we observed a discordant behavior with lesions increasing in size and other decreasing (Table 3). From a total of 16 meningiomas in those 4 patients, 6 showed tumor progression on the follow-up MRIs. 3/6 were located on the convexity; 2/6 were on the anterior skull base and 4/6 were posteriorly located. Only 2 of the 12 anteriorly located lesions showed tumor progression during follow-up.

Table 3
Discordant volume evolution in patients with multiple meningioma

Patient no	Age	Type of hormone	Signes and symptoms	No of meningiomas	Localisation	Clinical evolution	Initial volume (cc)	Final volume (cc)	Volume evolution
2	49	NOMAC	A/S	2	CONV ant CONV post	A/S	13.8	16.9	G
13	45	COMAC	A/S	6	MCF CONV (ant frontal) x4 MID (frontal)	A/S	3.5	3.3	ST
23	54	NOMAC	A/S	5	ACF x2 PCF CONV x2 (post)	A/S	17	24.6	G
25	74	NOMAC	A/S	3	ACF (jugum sph) ACF (ogm) MCF	A/S	3.1	3.5	G
NB meningioma in bold are those increasing in volume									

Overall, the percentage of tumor progression tends to be higher in the non-skull base tumor group compared to the skull base tumor group (respectively, 17.24% vs 8.3%; $p = 0.027$), without reaching significance. No correlation was found between patient age and evolution of the lesions.

Discussions

The association between exogenous sex hormones and meningiomas has long been a subject of debate, with epidemiological studies showing an absence of link or a weak link between oral contraceptive pills (OC) or hormone replacement therapy (HRT) and the risk of meningiomas. While no studies clearly established an association between contraceptives and meningioma[23–26], several studies suggested a positive correlation between HRT and an increased risk of meningiomas[26–28]. In a large cohort study, Jhawar et al. reported that the risk of meningioma associated with current hormone use was 2.48-fold for premenopausal women when compared with postmenopausal women who had never used HRT. The relative risk for postmenopausal women taking HRT was 1.86[28]. Conversely, two hospital-based case-control studies and one population-based case-control study found no association between HRT and meningioma[24, 29, 30]. A meta-analysis published in 2013 by Qi et al., concluded that HRT in postmenopausal women and an increased number of births were associated with an increased risk of meningioma, while oral contraception, age at menarche/menopause or age at first birth do not contribute significantly to the risk of developing meningiomas [26]. In a more recent meta-analysis, Benson et al. reported,, that there is an increased risk of meningioma among HRT users with a relative risk of 1.35 (95% confidence interval 1.21 to 1.49)[27].

Since 2008, attention has focused more specifically on CA, following a report from Froelich et al. that showed evidence of tumor regression after treatment discontinuation[10]. Since then, multiple case reports and small series were published suggesting a positive association between CA and the risk of meningioma. Only recently, a larger study based on the French social security database published by Weill et al., proved the link between CA and meningioma, with a risk of having a meningioma treated with surgery or radiotherapy in women pursuing high doses of CA multiplied by 6.6. The study also confirmed a strong dose-effect and a noticeable reduction in risk after treatment discontinuation[15].

While the link between CA and meningioma was thoroughly studied, there is far less available data regarding the link between CHA-NA and risk of intracranial meningioma [20, 31–33]. The first suspicion of a link between NA and meningioma was published in 2004 by Cottin et al. who described the case of a patient diagnosed with a large meningioma after being treated with NA for 16 years for pulmonary lymphangioleiomyomatosis [34]. In 2008 Shimizu et al reported the case of an 80 years old male incidentally diagnosed with a meningioma on a CT scan following a head injury [33]. The patient was treated with CHA for a benign prostate hypertrophy. The authors noticed a significant volume reduction on follow-up imaging after his treatment was changed to an alpha-2-blocker. In 2019, Passeri et al described a

series of 3 patients presenting with meningiomas and treated with NA, that showed spontaneous tumor regression after treatment discontinuation [20]. Champagne et al. also presented a case of a patient in which CHA and NA showed similar effect on meningiomas: growth under treatment and shrinkage after cessation of treatment[31]. In a recently published study of a consecutive series of patients between 1995 and 2008, Malaize et al. reported an increased number of patients diagnosed with progestin associated meningiomas over time. The rate of conservatively managed meningiomas also increased over time, with tumor regression seen in 29.6% of cases and tumor stability in 68.5% of patients [32].

In the present series, a clear favorable outcome of meningioma was observed after NA and CHA discontinuation, with most of the patients showing a regression in total tumor volume (50%) or volume stabilization (39.3%). By analyzing each of the 65 meningiomas, there was a higher percentage of tumor growth for midline and convexity lesions although these results were not statistically significant. Furthermore, 89% of our patients were asymptomatic at the end of the follow-up period with only one patient that worsened with a slight volumetric evolution on MRI.

Although there is a clear tendency towards regression or stabilization after NA and CHA discontinuation, similar to what is observed with CA, the percentage of tumor regression seems to be less important after cessation of CHA or NA [11, 15, 18, 32]. Bernat et al. reported a series of 12 CA-related patients, with tumor regression seen in over 90% of the patients. Malaize et al. showed that CA-related meningioma had a better answer to treatment discontinuation compared to CHA and NA-related tumors[11, 32].

Regarding tumor location, a predominance of anterior and middle skull base meningioma was observed, in accordance with previous findings[15, 18, 36]. Prolonged treatment (more than 10 years of progestin intake) seems to be linked to the occurrence of multiple meningioma and these patients appear to have a better clinical course than patients with single lesions. This is also in favor of the gradual appearance of new meningiomas under the influence of progestin intake. Discordant tumor evolution was seen in 4 patients with multiple meningiomas. Interestingly, in these patients, most of the growing meningiomas were either convexity or midline lesions, with a rather posterior location, while the majority of skull base and anterior convexity lesions showed significant regression.

A recent study by Peyre et al. that compared gene sequencing in progestin-associated meningioma vs a control group, showed a specific mutational landscape in progestins-related meningiomas, with a higher frequency of PIK3CA mutation (known to be associated with a more aggressive course in meningioma[37]) in hormone-related meningiomas[38]. When looking at NF2 and TRAF7 mutations (the 2 most frequent gene mutations in meningioma[37]), there was a significantly lower incidence of NF2 and a higher frequency of TRAF7 (40% vs 26%) when compared to the control group. Also, while TRAF7 were found to be associated with AKT1 and KLF4 mutations in the control group, in hormone-associated meningiomas there was a higher rate of isolated TRAF7 mutations.

Our results confirm the strong association between CHA-NA and meningioma. However, the results seem to be less encouraging than previously observed in patients treated by CA, with more patients showing tumor growth despite treatment discontinuation. Still, an important percentage of patients has a favorable response after treatment discontinuation. Therefore CHA-NA discontinuation and close observation should be, in our opinion, the first measure taken if urgent surgery is not needed. While the relationship between hormonal treatment and meningioma seems rather clear, the exact mechanisms of action are still to be determined. The long-term evolution after discontinuation of the drug is also unknown and requires larger scale studies to be properly determined.

Conclusion

Based on the present study, treatment with NA and CHA has a strong influence on meningiomas. However, the results seem to be less encouraging than previously observed in patients treated by CA. Still, the important rate of tumor regression or stabilization, as well as the good clinical outcome after cessation of treatment, is a strong argument for treatment discontinuation as the first measure in these patients. Although multiple meningiomas seem to be associated with a better outcome, close clinical and radiological follow-up is necessary, as discordant tumor courses might be seen. A thorough documentation of hormonal intake should be assessed in all meningioma patients, especially in women diagnosed with multiple meningiomas.

Declarations

Ethics approval: the study was approved by the local ethics committees from both institutions and validated by the national neurosurgical ethics committee (IRB00011687).

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Conflicts of interest: there are no conflict of interest in connection with this article.

Availability of data and material: the datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

Figure 1

Example of meningioma evolution after CHA-NA discontinuation - Picture A shows a T1 gadolinium sequence of the initial MRI in a 37yo asymptomatic patient, on a screening MRI after 10 years of continuous NA intake; picture B illustrates a significant shrinkage of the large left sphenoid wing meningioma, as well as for the sphenoidal and cavernous tumors on the right side, 29 months after treatment discontinuation.