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CLINICAL STUDY - PATIENT STUDY

Angiogenesis and expression of estrogen and progesterone receptors as predictive factors for recurrence of meningioma

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Abstract Meningiomas are benign tumors, with low rate of recurrence after surgery. The most important factor predicting recurrence is the extent of surgical resection; other factors have been studied with conflicting results. Angiogenesis, an important substratum for growth and spread of neoplasic cells, and the expression of estrogen and progesterone receptors (ER, PR), could play a role in the recurrence of meningioma. We evaluated 42 patients with meningioma diagnosis (confirmed by histopathology) treated exclusively by surgery between January 1995 and December 1999, and compared the recurring and non-recurring groups after a ten-year follow-up period. Recurrence was associated with several factors including vascular density (VD), cell proliferation index (CPI), ER, PR, and cyclin E (CE) tissue expression, as evaluated by immunohistochemistry. Complete surgical resection was achieved in 41% of patients. Recurrence of meningioma was found in 17 patients (40%). Median ± standard deviation (SD) of recurrence time was 32 ± 5 months. When recurrence versus no recurrence was compared, mean ± SD of VD and CPI were 9 ± 3.6 and 607.6 ± 233 (40×/10 fields) respectively. Tissue expression was positive for ER, PR, and CE in 28, 62 and 91% of patients, respectively. The sole significant recurrence-associated factors were extent of resection ($P = 0.003$) and VD ($P = 0.004$). ER, PR, and CE-tissue expression were not statistically significant. The most important factor associated with meningioma relapse was vascular density, independently of hormonal status and extent of surgical resection. Patients with a high risk of recurrence could benefit from additional treatment.

Keywords Meningioma · Recurrence · Angiogenesis · Estrogen receptor · Progesterone receptor · Cell proliferation

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Background

Meningiomas account for approximately 25% of all primary intracranial neoplasms; most of them are benign and their incidence increases with age [1]. After surgical treatment, 20% of those reported as complete resection show recurrence within 10 years and more than 80% relapse after partial resection [2]. Thus, despite its lack of specificity, the most reliable predictive factor of meningioma recurrence remains the extent of surgical resection [3]. Several other clinical and histopathologic features (i.e. tumoral hemosiderin deposits, sheeting pattern, prominent nucleoli, mitosis, micronecrosis, moderate nuclear pleomorphism, and peritumoral edema) have been associated with recurrence [4]; however, their relatively low

frequency renders them unsuitable as sole predictors of meningioma relapse.

Recently, angiogenesis has been recognized to have an important role as a mechanism regulating growth and the spread of neoplasic cells by inducing a more efficient vascular supply for growing tumors [5]. Neoplasms could exhibit low angiogenic ability during pre-malignant phases; hence, changing their phenotype towards a cell type able to produce angiogenic factors, which may degenerate to an invasive tumor with the ability to spread, generate metastases, and relapse after treatment.

Steroid hormone receptors act as transcription factors that mediate the biological effects of steroids by regulating gene expression. Previous studies have shown the presence of estrogen (ER) and progesterone receptors (PR) in approximately 10 and 65% of meningiomas, respectively [6–12]. The higher incidence of meningiomas in women, their growth during pregnancy and luteal phase with subsequent decrease after delivery, and their association with breast carcinoma suggest that this type of tumor could be hormone-dependent [13–15]. Furthermore, both in-vitro and in-vivo studies have shown that growth of meningiomas can be manipulated by progesterone and anti-progesterone drugs, and that there is a higher concentration of PR in recurrent than in primary meningiomas [9, 16–18], suggesting a role of PR in their development. However, the role of ER and PR as predictive factors of recurrence in meningiomas has not been settled.

During the normal cell cycle, progression through various stages is regulated by the tightly controlled actions of cyclin-dependent kinases and cyclins [19]. Cyclin E (CE) is an important regulator of the G1/S phase transition and induces accelerated S-phase entry [20, 21]. Deregulation of CE may also induce chromosome instability by triggering inappropriate initiation of DNA replication and centrosome duplication [22–24]. High expression of CE in other tumors, for example breast and bladder cancer, has been related to worse prognosis and shorter recurrence-free survival [25, 26], but the role of CE in prediction of meningioma relapse has not been established.

The objective of this study was to evaluate the association of cell proliferation index (CPI), vascular density (VD), ER, PR, and CE -tissue expression with recurrence of meningiomas after surgical resection.

Materials and methods

Patients and samples

This was a nested case–control cohort study carried out at the Instituto Nacional de Neurologia y Neurocirugia (INNN, a teaching referral hospital in Mexico City, Mexico). Tumoral tissue from 42 patients who underwent surgery between January 1995 and December 1999 was studied. Patients who had received chemotherapy or radiotherapy prior to surgery were not included.

Clinical follow up

Follow up was carried out for a period of ten years. Recurrence was confirmed by imaging studies. In this study, 17 patients presented recurrence; the remaining 25 patients without evidence of recurrence were taken as controls. The extent of surgical resection was measured according to the Simpson scoring system [3]. Tumor location and weight were recorded. Patients with radiation-related neoplasm according to DeMonte [27] were excluded.

Histopathologic study

A portion of the biopsy was fixed in 10% formaldehyde and 5-μm paraffin-embedded slices were obtained. Histologic type and tumoral degree were determined on hematoxylin-eosin stained specimens according to the WHO 2002 classification [28].

Vascular density and cell proliferation

Immunohistochemical staining was performed using the avidin–biotin–peroxidase method and counter-stained with hematoxylin–eosin. Tissue samples were incubated for one hour at room temperature with polyclonal mouse or rabbit antibodies against Factor VIII-related antigen (or Von Willebrand factor) as endothelial cell marker (Dako, USA), and against proliferating cellular nuclear antigen (PCNA) as a marker of DNA synthesis (Dako). Indexes of both vascular density and cell proliferation were obtained by quantification of the number of FVIII-positive capillaries (at 40×) and PCNA-positive neoplasic cell nuclei (at 40×) in ten different fields. These analyses were made independently by two pathologists without previous knowledge of the source of the specimen.

Estrogen and progesterone receptors

For immunohistochemistry of hormone receptors, monoclonal antibodies 6F11 and PGR312 were used for ER and PR, respectively (Novocastra Laboratories, Newcastle, UK). Antigen retrieval was carried out as described elsewhere [29]. All antibodies were diluted at 1 g/ml, and detected with a peroxidase-polymer based detection kit (PowerVision+, Immunovision Technologies, Daly City, CA, USA) according to manufacturer's instructions.

Cyclin E

Cyclin E (CE) tissue-expression was analyzed by use of an anti-CE monoclonal antibody (Novocastra Laboratories). Slides were pretreated with citrate buffer in a microwave oven. The antibody was diluted to 1:40, added on the slide, and incubated at room temperature for 1 h. All the following procedures were done according to standard procedures with an EnVision kit (Dako). The CE labeling index was defined as the percentage of tumor cells displaying nuclear immunoreactivity and was calculated by counting the number of CE nuclear-stained tumor cells per 1,000 tumor cells. A single representative section from each sample was surveyed microscopically for at least two areas of the highest CE intensity of positive cells. Cell counts were performed for least five fields in these areas. According to the percentage of the cells showing the nuclear staining pattern, tumor samples were judged to be negative (<2%) or positive (≥2%) as described elsewhere [30].

Statistical analysis

Univariate analysis was used to associate age, gender, histological type and score, extent of resection, tumor weight, tumor location, VD, CPI, ER, PR, and CE-tissue expression with recurrence. Mean values were compared with the two-sample independent *t*-test. ANOVA was used for bivariate correlation for parametric values. Non-parametric variables were compared with the Fisher's exact and χ^2 tests when indicated. Statistical significance was determined with $P < 0.05$ in a two-sided test. SPSS software package (version 14.0; SPSS, Chicago, IL, USA) was used for data analysis.

Results

Clinical characteristics

Complete resection was achieved in 41% of the total cohort. Clinical data for patients with meningioma according to the presence of recurrence are shown in Table 1. No significant differences between groups were found with regard to age at diagnosis ($P = 0.079$), gender ($P = 0.74$), tumor location ($P = 0.32$), or tumor weight ($P = 0.57$). Mean ± standard deviation (SD) time of recurrence was 32 ± 20 months. Extent of resection was significantly related with meningioma relapse ($P = 0.003$). No differences in recurrence were found between complete and partial resection as stated at the original surgical report ($P < 0.3$).

Table 1 Patient characteristics according to meningioma recurrence

Variable	No recurrence ($n = 25$)	Recurrence ($n = 17$)	*P*
Age at diagnosis			0.079
(Mean ± SD)	52 ± 3 years	44 ± 4 years	
Gender (%)			0.735
Female	64	59	
Male	36	41	
Ratio F:M	1.7:1	1.4:1	
Location (%)			0.324
Frontal	26	23	
Sphenoidal	22	12	
Petroclival	13	12	
Other	39	53	
Surgical resection (%)			0.003
Complete	60	12	
Partial	40	88	
Tumor weight			0.568
(Mean ± SD, g)	38 ± 10	47 ± 12	
Recurrence time			
(Mean ± SD, months)		32 ± 5	

SD, standard deviation; Ratio F:M, ratio female:male; g, grams

Histopathological details

Meningothelial–histological type was found in 45% of patients. A low grade of differentiation was observed for 91% (38/42) of meningiomas. Mean ± SD for cell proliferation was 608 ± 233 (40×/10 fields). Table 2 shows the histopathological characteristics of samples according to recurrence. No differences were found between groups according to the grade of differentiation ($P = 0.63$) or type ($P = 0.24$), or for cell proliferation ($P = 0.121$).

Vascular density index

Mean ± SD of VDI was 9 ± 3.6 (40×/10 fields). Differences in VDI among groups with and without recurrence were significantly related with recurrence (mean ± SD, 11 ± 6 vs. 7 ± 4 respectively; $P = 0.004$) (Table 2; Fig. 1). These differences remained significant (mean ± SD, 12.8 ± 3.4 vs. 5.5 ± 3.5 respectively; $P = 0.038$) for the subgroup analysis of patients with complete resection status ($n = 17$), with and without recurrence (Fig. 2).

Hormone receptors and cyclin E

Tissue expression was positive for ER, PR, and CE in 28, 62 and 91% of patients, respectively. However, differences

Table 2 Histological characteristics of meningiomas according to recurrence

Variable	No recurrence ($n = 25$)	Recurrence ($n = 17$)	P
Histological type (%)			0.244
Meningothelial	52	35	
Transitional	20	26	
Fibroblastic	12	18	
Atypical	8	12	
Metaplasic	4	6	
WHO grade (I/II)	23/2	15/2	0.63
Cell proliferation index (Mean ± SD)	527 ± 87	747 ± 108	0.121
Vascular density (Mean ± SD)	7 ± 1	12 ± 1	0.004
Estrogen receptors			0.45
Positive	35	17	
Negative	65	83	
Progesterone receptors			0.17
Positive	65	57	
Negative	35	43	
Cycline E			0.85
Positive	90	92	
Negative	10	8	

SD, standard deviation; WHO, World Health Organization

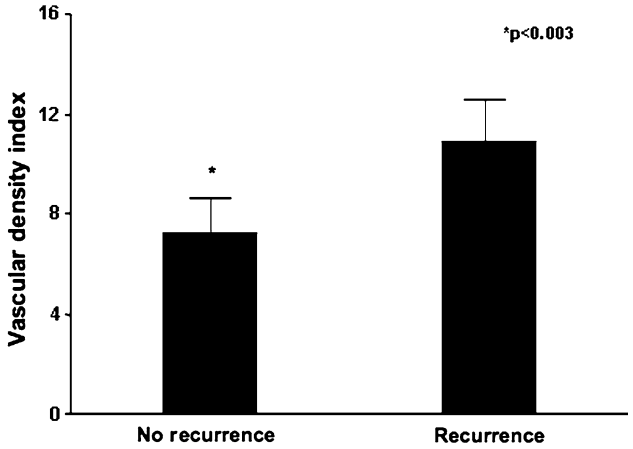

Fig. 1 Vascular density in meningiomas according to their recurrence rate

between groups showed no statistical significance, ER ($P = 0.45$), PR ($P = 0.17$) and CE ($P = 0.85$) (Table 2).

Discussion

Despite the usually benign nature of meningiomas (91%), their long-term prognosis is tainted by a high recurrence rate [31]. Relapse is present in 12–70% of patients, even in cases reported as "totally resected" by surgery [32]. Extensive research to find prognostic markers has been conducted [4, 33–38]; however, most of these methods have not gained acceptance as practical guidelines. In our study we found no differences enabling prediction of recurrence on the basis of age at diagnosis, gender, tumor location, tumor weight, histological score or type and cell proliferation index. Moreover, contrary to our initial hypothesis, tissue-expression of estrogen and progesterone receptors and cycline E were not associated with recurrence. As expected, this association was significant only in relation to the extent of resection ($P < 0.003$).

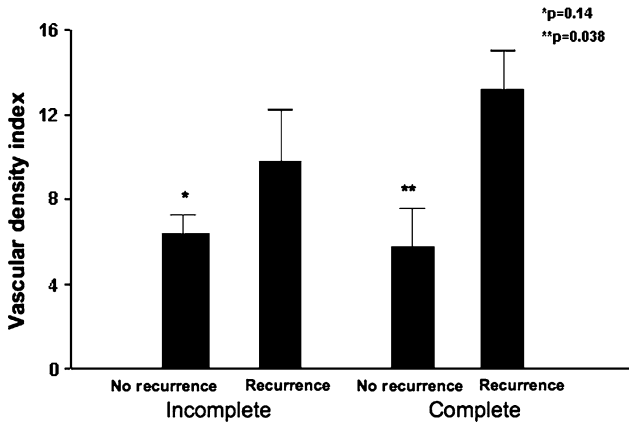

Fig. 2 Vascular density in meningiomas according to their recurrence rate in patients with complete and incomplete resection

In contrast with the above results, index of vascular density provided a quantitative measure of angiogenesis in a variety of pathologic processes, including neoplasia. This has been extensively analyzed in several malignancies and is considered a useful prognostic marker in many forms of cancer [39]. Several studies have been performed in order to quantify vascular density in meningiomas, by using endothelial markers such as FVIII, CD31, and CD34 [12, 40–46]. Some authors have found correlation between vascular density and tumor grade [42, 43, 46]. The major finding in our study was the association between vascular density index and recurrence of meningiomas ($P < 0.001$). Even in subgroup analysis of patients with meningioma reported as totally resected, VDI was a reliable predictor of recurrence ($P < 0.038$).

The findings of this study reveal a higher degree of involvement of the vasculature in recurrent versus non-recurrent meningiomas, suggesting a more active angiogenesis process in the former. Vessel neoformation is regulated by the balance of angiogenic stimulating and inhibiting factors [5, 47], and tumoral growth, neovascularization, and edemagenesis, which have been strongly associated with different growth factors in several

neoplasias. In the case of meningioma, growth factors have also been evaluated [48–50].

Inhibiting angiogenesis has become an increasingly attractive approach for treating recurrent meningiomas [51], because vascular-endothelial-growth factor (VEGF) and its receptor (VEGFR) are expressed by meningioma cells, with the level of expression increasing with tumor grades, VEGF and its receptor should be regarded as key angiogenic regulators [41, 44, 52–54]. VEGF also plays an important role in the formation of peritumoral edema, contributing to the morbidity of these tumors [41, 44, 52, 53]. Several studies have demonstrated that VEGF-A levels in meningiomas are associated with the extent of edema-genesis [44, 52, 55]. In another study, Yamasaki et al., reported a significant correlation between VEGF protein expression and recurrence of benign meningiomas [56]. This suggests that inhibitors of VEGF and VEGFR are promising agents for treatment of meningiomas, with the potential not only to inhibit angiogenesis, but also to reduce peritumoral edema. Moreover, hypoxia plays a role in tumor development, angiogenesis, and growth in many different human cancers, with invasion, apoptosis, chemoresistance, resistance to antiangiogenic therapy, and radiation resistance all having hypoxic mechanisms as their main regulator. Thus, the extent of the effect of hypoxia in these processes, including angiogenesis, makes it an attractive target for therapy of meningioma [57].

Our report is limited by being a retrospective analysis; however, we describe valuable information regarding the role of angiogenesis in predicting recurrence in a long-term follow up of patients with meningioma.

Conclusions

In patients with surgical resection, the most important factor associated with meningioma relapse was the degree of vascular density, irrespective of hormonal status and extent of surgical resection. Patients with a high risk of recurrence could be candidates of additional therapeutic measures.

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