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Prognostic Significance of Steroid Hormone Receptors and DNA Content in Meningiomas

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To investigate the prognostic utility of Estrogen and progesterone receptors (ER, PR) as part of the classical nuclear Steroid hormone receptors superfamily markers and DNA content in a representative intracranial meningiomas. We have immunohistochemically studied the expression of ER and PR as well as DNA content of meningioma collected retrospectively and studied the Correlations between every studied prognostic parameter (age, sex, menopause, nuclear grades, PR and ER). Tumor specimens were immunohistochemically examined with antibodies to ER and PR. A computerized color image analyzer was used to count Feulgen immunostained nuclei for DNA content. The immunohistochemical study of Meningioma specimens showed that 70% were positive immunoreactivity for progesterone receptor while 30% were positive immunoreactivity for oestrogen receptors. The DNA content determined by image cytometry showed, aneuploidy in atypical and malignant meningiomas compared to benign meningiomas. A significant correlation at the 0.01 level (2- tailed) between the nuclear grading and progesterone positive immunoreactivity using the Spearman's test. Progesterone and Estrogen steroid hormone receptors with the nuclear DNA ploidies showed a significant association with tumor grade, play a significant role in Meningioma tumour pathogenesis, supporting the possibility of both prognostic and predictive utilities as well as their application as a test for grading.

Key words: Meningioma, estrogen, progesterone, receptors, DNA, ploidy

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INTRODUCTION

Histologic classification of meningiomas was correlated with their proliferative fraction and DNA ploidy using immunohistochemistry and cytometry to differentiate histologically atypical meningiomas from benign ones. The prognosis of meningioma depends upon clinical factors histopathology and grading of the tumour (DeLellis *et al*., 2004). Meningiomas are tumors that accounting nearly up to 20% of all central nervous system tumors according to the well established scheme by the 2000 World Health Organization (WHO). Meningioma is generally benign well circumscribed and a slowly growing tumor. It can be surgically removed in most cases and surgery has been the only available treatment. The outcome of meningioma was more favorable in patients younger than 50 years and in those with clinical symptoms for less than one year. However, some tumors are inoperable because of the poor clinical condition of very old patient or due to malignant aggressiveness invasion of bone and/or blood vessels (Fahlbusch and Schott, 2002). Great progress has been made in the molecular genetics study of meningiomas using panels of tumour markers (Kleihues *et al*., 2000). The genetic heterogenecity can be used for detailed characterization and subsequently subtyping the most aggressive meningioma (DeLellis *et al*., 2004). The objective of this study was to assess whether steroid hormone receptors expression contributes to the development and progression of different meningioma and to investigate any differences in the expression of ER and PR immunohistochemically in different cases of meningioma. The expression of oestrogen and progesterone receptors in meningioma remains a fascinating phenomenon which requires further investigation (Blankenstein *et al*., 2000). It is not yet known whether in classic meningioma their cytogenetic abnormalities would be predictive of either aggressive or malignant transformation (DeLellis *et al*., 2004).

Numerous studies have reported the predictive value of various patterns of meningioma by using DNA ploidy analysis and cytometry studies Cytometry, is the science of determining the relative optical concentration of intracellular substances in cell populations in Video-based image analysis techniques. These methods allow the relatively rapid and semiautomatic measurement of Feulgen-stained histologic slides, in a more efficient manner.

The objective of this research is to help to define and going onto the clinical behaviour to provide a rationale basis for meningioma pathogenesis. To access a possible sex steroid hormone dependence of meningioma progression. we have immunohistochemically studied the expression of estrogen and progesterone receptors as well as DNA content of meningioma with a correlations between every studied prognostic parameter (age, sex, menopause, nuclear grades, PR and ER).

MATERIALS AND METHODS

Twenty eight meningioma were entered into this study between January 2003 and January 2004, Cases were collected from the Pathology Department, Kasr Elaini Hospital, Cairo University.

Histopathological study: Formalin fixed meningioma specimens, paraffin embedded tissue and 5 microns sectioned for routine heamatoxylin and eosin stain. Examination for tumor subtyping and grading, the classification was done according to the criteria presented by the latest 2000 WHO classification system. Nuclear grade I showed atypia; grade II showed atypia and mitosis and grade III was the anaplastic meningioma with microscopic brain invasion, mitotic rate (>or = 4/10 high-power fields), the presence of at least 3 of 4 morphologic variables (Sheeting, Hypercellularity, macronucleoli and small cells).

The immunohistochemical study: Immunohistochemical study of tumor was done for the tissue sectioned and immunostained using the streptavidin/peroxidase method and using monoclonal antibodies for estrogen receptor (ER) and progesterone receptor (PR). Analysis was scored in a semiquantitative fashion incorporating both the intensity and distribution of specific staining (SCORE). The staining of PR and ER of meningioma was interpreted according of percentage of stained cells as: 3+ or Diffuse staining (>60% of cells stained), 2+ or Regional staining (5-60% of cells stained), 1 + or Focal positive staining (<5% of the cells) and Negative staining (no stained cells).

Cytometry of DNA

Feulgen stain: The Feulgen staining reaction specifically stains the nuclear DNA to give specific blue staining. Nucleoli and cytoplasm should show no staining. The mean nuclear size (μm^2) of tumor cells was estimated using computer-based image analysis on 5 μm histological sections. Tumor ploidy was quantitated by image cytometric DNA measurement (Leica Quin 500 DNA cytometry software) from 50 μm Fuelgen-stained tissue sections. Three ploidy categories were used diploid, non diploid (near diploid) and true aneuploid more than 5% of the neoplastic cells exceeded the 5C value (DNA content more than 5 sets of 23 chromosomes).

RESULTS AND DISCUSSION

Although the study population included a wide range of patient ages (range 23 to 70 years, median 45 years), 16 women (4 premenopausal and 12 postmenopausal) and 12 men comprised the study groups (Table 1). The most common meningioma was meningothelial and anaplastic histopathological types (Table 1) and more than 50% were of nuclear grade III (Table 2).

The histopathological classification was done according to the criteria presented by the latest 2000 World Health Organization. Nuclear grade I showed beginity; grade II showed atypia and mitosis and grade III was the anaplastic meningioma Pre = premenopausal; Post = postmenopausal (Fig. 1 and 2).

Immunohistochemical and cytometric results: Table 3 showed corresponding DNA content and the immunohistochemical estrogen and progesterone receptors immunoreactivities, 19 cases (70%) showed positive immunohistochemical reactivity to (PR) and 9 cases (30%) showed positive immunohistochemical reactivity to (ER).

The staining of PR and ER of meningioma was interpreted according of percentage of stained cells as: 3+ or Diffuse staining (>60% of cells stained), 2+ or Regional staining (5-60% of cells stained), 1 + or Focal positive staining (<5% of the cells) and Negative staining (no stained cells).

Figure 3 represented the measured DNA ploidy of the studied cases and three ploidy categories were used diploid, non diploid (near diploid) and true aneuploid more than 5% of the neoplastic cells exceeded the 5C value (DNA content more than 5 sets of 23 chromosomes) showed that 14 cases were true aneuploid (50%), 8 cases were in the diploid region (28%),While only 6 cases were non diploid (22%).

There is a significant correlation between the DNA content of the studied meningiomas cases and the nuclear grades in which more than 50% of the cases were of grade II and III. Therefore, atypical and malignant meningiomas should be distinguished from benign meningiomas by histopathologic examination and confirmed by studies on their DNA ploidies.

Hsu *et al.* (1997) studied the prognostic considerations of progesterone and estrogen receptors in meningiomas. Despite the availability of clinical and pathologic parameters of prognosis (age, sex, menopause, nuclear grade, PR and ER), the behavior of an individual meningioma may be difficult to predict in a recent review of gross totally resected meningiomas (Perry *et al.*, 1998).

Table 1: Clinical data and histopathological tumor types in all studied cases

Case	Age	Sex	Menopausal	Histopathology	Grade (G)
1	38	♂	-	Meningothelial	G I
2	49	♂	-	Meningothelial	G I
3	38	♀	Pre	Anaplastic	G III
4	66	♀	Post	Atypical	G II
5	56	♀	Post	Fibrous	G I
6	61	♀	Post	Anaplastic	G III
7	43	♂	-	Anaplastic	G III
8	63	♂	-	Atypical	G II
9	68	♀	Post	Anaplastic	G III
10	41	♀	Pre	Meningothelial	G I
11	52	♀	Post	Atypical	G II
12	69	♀	Post	Anaplastic	G III
13	70	♂	-	Meningothelial	G I
14	23	♂	-	Anaplastic	G III
15	37	♂	-	Psammomatous	G I
16	48	♂	-	Meningothelial	G I
17	39	♀	Pre	Anaplastic	G III
18	65	♀	Post	Atypical	G II
19	55	♀	Post	Psammomatous	G I
20	62	♀	Post	Anaplastic	G III
21	42	♂	-	Anaplastic	G III
22	64	♂	-	Atypical	G II
23	66	♀	Post	Anaplastic	G III
24	40	♀	Pre	Meningothelial	G I
25	50	♀	Post	Atypical	G II
26	67	♀	Post	Anaplastic	G III
27	69	♂	-	Meningothelial	G I
28	24	♂	-	Anaplastic	G III

Table 2: Tumor nuclear grade percentage in all studied cases

Gender	Grade I	Grade II	Grade III	Total
Male	6 (50%)	2 (16%)	4 (33%)	12 (100%)
Premenopausal female	2 (50%)	-	2 (50%)	4 (100%)
Postmenopausal female	2 (16%)	4 (33%)	6 (56%)	12 (100%)
Total cases	10 (35%)	6 (21%)	12 (42%)	28 (100%)

In terms of diagnostic histopathology clinically and biologically more interesting are the strong capacity for rapid progression, creating a diagnostic and therapeutic dilemma. Immunohistochemical assessment of progesterone receptor (PR) protein is used as a prognostic indicator for adenocarcinoma of the breast; tumors positive for progesterone receptor (PR) have a better prognosis than those that are negative for the protein. Binding of monoclonal antibodies may depend on the conformational state of the PR (Traish *et al.*, 1994).

The abundant expression of progesterone receptors (PR) in 70% of human meningiomas is well established (Fig. 1 and 2). It is unknown however, how (PR) expression is regulated especially since estrogen receptor (ER) are virtually less expressed in 30% these tumors. We find that the majority of meningiomas are immunoreactive for PR (Table 3), in agreement with other authors Perrot-Applanat *et al.* (1992) and Tesch *et al.* (1993) and are positively associated with breast cancer. However, unlike breast cancer, meningiomas are much more commonly positive for progesterone receptor than for estrogen receptors, this was also reported by Emry *et al.* (1984).

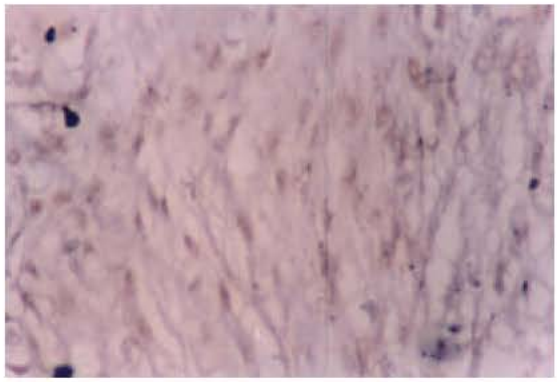

Fig. 1: Grade I meningioma showing marked nuclear staining for progesterone receptor (immunohistochemical stain x 400)

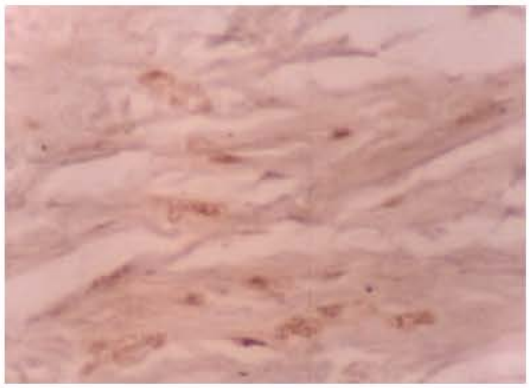

Fig. 2: Grade I-II meningioma showing moderate nuclear staining for progesterone receptor (immunohistochemical stain x 400)

In our results the anaplastic grade III meningiomas was 43%, atypical grade I meningiomas 21% and benign meningiomas was 36% (Table 2). The studies reported by Boker *et al*. (1985) and Hilbig and Barbosa (1997) showed rates of recurrence for atypical, anaplastic, as well as benign meningioma following incomplete surgical resection are high. The recurrence rate of (13%), higher in atypical (42.5%) and anaplastic (45.5%) than in typical (3.78%). They may also show atypical or anaplastic features (May *et al*., 1989; Jaaskelainen *et al*., 1986). The reported percentage of more malignant tumors varies, according to investigators from 0.9 to24% (Hilbig and Barbosa, 1997).

At the nuclear RNA level, ER splice variants occur in meningioma but these appear not to be involved in the apparently outonomous PR expression. In an earlier study because other ER-inducible proteins were either not expressed at a very low level compared to their expression in breast cancer (Cathepsin-D) Lesch *et al*. (1987) and

Table 3: Immunohistochemical and cytometric results in all studied case

Case	Progesterone	Estrogen	DNA ploidy
1	+++	-	Diploid
2	-	+	Non Diploid
3	+		Aneuploid
4	-	+	Non Diploid
5	+++	-	Diploid
6	+	-	Aneuploid
7	-	+	Aneuploid
8	+++	-	Aneuploid
9	-	+	Aneuploid
10	+++	-	Aneuploid
11	+++	-	Aneuploid
12	+	-	Non Diploid
13	+	-	Non Diploid
14	+	-	Aneuploid
15	+++	-	Diploid
16	-	+	Non Diploid
17	+	-	Aneuploid
18	-	+	Non Diploid
19	+++	-	Diploid
20	+	-	Aneuploid
21	-	+	Aneuploid
22	+++	-	Aneuploid
23	-	+	Aneuploid
24	+++	-	Aneuploid
25	+++	-	Aneuploid
26	+	-	Non Diploid
27	+	-	Non Diploid
28	+	-	Aneuploid

Yu *et al*. (1982) have postulated that the autonomous in PR promotor-related rather ER related and have studied PR expression in cultured meningioma cells (Table 3).

Deprez *et al*. (1995) and Lesch *et al*. (1987) suggested that a lower incidence of progesterone receptor positivity may be seen in anaplastic meningioma. This support our results (Table 3, Fig. 1 and 2), with a significant correlation according to spearman`s test (Table 4).

Immunohistochemical determination of progesterone receptor (PR) protein (Table 3, Fig. 2 and 3) is used to predict prognosis and response to hormonal therapy. The presence of progesterone receptor is associated with better over all survival according to Carrol *et al*. (1993). Therefore increased cell proliferation activity determined by Ki-67 (MIB-1) Perry *et al*. (1998) found that MIB-1 LI in a useful adjunct for routine histologic evaluation of meningiomas and appears to be of greatest value in the evaluation of tumors exhibiting borderline atypia. This is supported by our results in which observed high frequency of progesterone and estrogen in the tumor tissue support the possibility of their application as a test for grading and for adequate treatment choice.

Steven *et al*. (1991) initiated a study on long term oral therapy of unresectable meningiomas with the antiprogesterone Mifepristone. Fourteen patients received Mifepristone in daily doses of 200 mg for periods ranging from 2 to 31 months (> 6 months in 12 patients). Five patients have shown signs of objective response (reduced tumor measurement on computerized

Table 4: Correlations between every studied prognostic parameter age, sex, menopause, nuclear grades PR and ER, (2-tailed) using the spearman`s statistical test

Test	Statics		PLODP	SEX	MENOP	GRADE	GRADE 2	PR	ER
Spearmans r	PLODP	Correlation coeffi	1.000	0.059	-0.218	0.489*	0.354	0.258	-0.258
		Sig. (2-tailed)	0	0.766	0.417	0.008	0.065	0.185	0.185
		N	28	28	16	28	28	28	28
	SEX	Correlation coeffi	0.059	1.000	0	0.230	0.167	-0.091	0.091
		Sig. (2-tailed)	0.766	0	0	0.238	0.397	0.644	0.644
		N	28	28	16	28	28	28	28
	MENOP	Correlation coeffi	-0.218	0	1.000	0.136	0.000	0.333	-0.333
		Sig. (2-tailed)	0.417	0	0	0.615	1.000	0.207	0.207
		N	16	16	16	16	16	16	16
	GRADE	Correlation coeffi	0.489*	0.230	0.136	1.00	0.921*	0.126	-0.126
		Sig. (2-tailed)	0.008	0.238	0.615	0	0.000	0.522	0.522
		N	28	28	16	28	28	28	28
	GRADE 2	Correlation coeffi	0.354	0.167	0.000	0.921*	1.000	0.091	-0.091
		Sig. (2-tailed)	0.065	0.397	1.000	0.000	0	0.644	0.644
		N	28	28	16	28	28	28	28
	PR	Correlation coeffi	0.258	-0.091	0.333	0.126	0.091	1.000	-1.000*
		Sig. (2-tailed)	0.185	0.644	0.207	0.522	0.644	0	0.000
		N	28	28	16	28	28	28	28
	ER	Correlation coeffi	-0.258	0.091	-0.333	-0.126	-0.091	-1.000*	1.000
		Sig. (2-tailed)	0.185	0.644	0.207	0.522	0.644	0.000	0.
		N	28	28	16	28	28	28	28

* Correlation is significant at the 0.01 level (2-tailed)

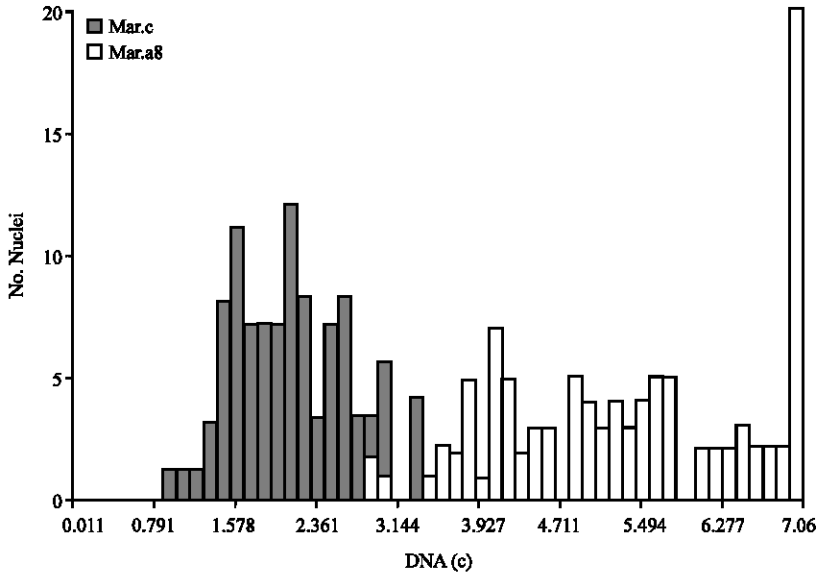

Fig. 3: DNA ploidy was in the hyperpolyploid region between 4c-16c (true aneuploid with the DNA content are more than 5 sets of 23 chromosomes)

tomography scan or magnetic resonance image). Three have also experienced subjective improvement (improved extraocular muscle function or relief from headache). Tumor regression noted in five of the 12 patients. Two of the three patients who directly developed progressive disease while on Mifepristone were those with the most malignant histologies. Given the potential benefit of antiprogestin treatment and the occurrence in meningiomas of a protein capable of binding to the estrogen. Responsive elements, previous clinical studies with Mifepristone have concentrated on short-term therapy in premenopausal patients (Couzine *et al*., 1986; Nieman *et al*., 1987).

However given the importance of cell image analysis as other modalities reported to be of potential prognostic value, which if any of these methods will come to be used in the routine diagnostic workup, In our study 28% (8 cases) were non diploid and 50% (14 cases) were aneuploid, showing a positive relationship with the meningioma grades (Fig. 3 and Table 3) and that most of the studied cases were in the hyperpolyploid region. Meningiomas remains to be determined-likewise, a number

of chromosomal abnormalities have been detected in great frequency in atypical and malignant meningiomas. Identification of the relevant genes involved in these alterations would as doubt improve our understanding of the biology of meningioma.

Perry *et al.* (1998) found strong associations between microscopic brain invasion, mitotic rate (>or = 4/10 high-power fields), the presence of at least 3 of 4 morphologic variables (Sheeting, Hypercellularity, macronucleoli and small cells), they assessed the prognostic value of DNA flow cytometry, MIB-1 labeling and P53 protein expression.

We found a significant correlation at the 0.10 level (2-tailed) between nuclear grading and progesterone positive reactivity using Spearman's test Table 4, this has been reported by Bouillot *et al.* (1994) Lesch and Gross (1987) Nagashima *et al.* (1995) Perrot-Applanat *et al.* (1995). It is tempting to specula that this factor underlies the relative lack of higher grade tumors among females. Christensen *et al.* (1983) and Scarpelli *et al.* (1989) evaluated quantitative recurrent meningioma by cell image analysis and reported their potential prognostic value. Perry *et al.* (1998) studied DNA in meningioma by cytometry in completely resected primary meningiomas, suggesting that cytometry and P53 immunohistochemistry provides useful prognostic information.

CONCLUSIONS

The study showed that sex steroid hormones and their receptors play an important role in the pathogenesis of meningioma tumor, these results must therefore be considered preliminary and will require confirmation in large controlled studies. Our results suggest that evaluation of cell proliferation using DNA ploidy, integrated with standard histopathology, can provide better information for a correct grading of meningiomas. only to a subset of patients failing conventional radiation therapy. We conclude that the majority of meningiomas showed progesterone receptors and the PR status may be a useful prognostic tool if associated with other histological features.

Increased appreciation of the role of steroidal hormones as potential prognostic factors in specific situations may lead to new therapeutic avenues. Similarly, while a significant direct correlation between the presence of steroid hormone receptors and response to hormonal therapy has been reported in other studies, there is a general agreement that endocrine treatment is only slightly efficacious in the management of advanced meningioma and it should be reserved for palliation therapy.

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