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ORIGINAL ARTICLE

Hormone receptors in benign intracranial meningiomas

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Summary

Purpose: *Although some embryologic data suggest that the neural crest elements, which are not a target tissue for estrogen and progesterone, participate in the forming of meningothelial cells, meningiomas show hormone receptors. The aim of this study was to investigate the estrogen (ER) and progesterone receptors (PR) content of benign meningiomas (WHO grade I) which were completely resected.*

Materials and methods: *Paraffin-embedded tissue sections of 30 intracranial meningiomas were examined immunohistochemically using monoclonal antibodies for ER and PR.*

Results: *All 30 (100%) tumor samples were ER-negative. Seventeen (57%) of them were positive for PR. These receptors were found in 8 of 17 (47.50%) tumors in female patients and in 9 of 13 (69.23%) tumors in male patients (Mann-Whitney $p < 0.05$). Age, localization of tumors and histological subtype did not correlate with PR status.*

Conclusion: *This study demonstrated complete absence of ER in benign meningiomas. In contrast, PR were positive in more than half of the patients. PR positivity was significantly higher in male patients*

Key words: estrogen receptors, immunohistochemistry, meningioma, progesterone receptors

Introduction

Meningiomas are common intracranial slow-growing neoplasms. Surgical removal is the treatment of choice [1,2]. Recurrence rate, even in totally resected benign tumors (World Health Organization – WHO - grade I) is approximately 5% within the first 5 years, and 15-20% within the first 10 years [3-6]. Adjuvant radiotherapy and systemic chemotherapy have not given better results in the management of meningiomas [6-10].

Some embryologic data suggest that neural crest elements participate in the forming of meningothelial cells [11,12]. By immunohistochemical methods it is shown that meningioma cells display both mesenchymal and epithelial features. Epithelial membrane antigen (EMA) [13-15] and vimentin [16, 17] staining are present in all meningiomas. Although they do not arise from a tissue normally thought to be a target tissue for estrogen and progesterone, meningiomas show a number of epidemiologic and clinical features which suggest that female sex hormones can play a role in their development. For example, higher incidence of meningiomas is found in females [13], rapid progression of symptoms and increase in size occurs during pregnancy [18] and during the luteal phase of the menstrual cycle [19] and there is also significant association of meningiomas with obesity and breast carcinoma [20,21].

In recent years, the development of monoclonal antibodies specific for steroid hormone receptors has enabled the detection of ER and PR with direct visualisation in tissue samples of meningiomas [21-24].

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Although there is a general agreement that the majority of meningiomas contain PR but not ER, the importance of receptor status in the progression of meningiomas is unknown.

The aim of the present study was to investigate immunohistochemically the ER and PR content of benign meningiomas (WHO grade I) which were completely excised.

Materials and methods

Surgical specimens were obtained from 30 consecutive patients with intracranial meningiomas operated in the Department of Neurosurgery of Clinical Hospital Center, Zemun, during the period 2001-2002. Tissue samples of meningiomas were obtained from the peripheral area of the tumors with no thermal damages caused by instruments, and without necrosis and bleeding. All tumors were totally removed. Tumor tissue samples were fixed in formalin and embedded in paraffin using standard methods. Sections (5 nm) were stained with hematoxylin and eosin, periodic acid, Schiff and Gordon sweet reticulin. None of the following features were present: invasion into the brain parenchyma or bone, sheeting of tumors cells, cellular and nuclear pleomorphism, increased cellularity and/or elevated mitotic rate. Tumors were classified according to the new classification system of WHO as benign (WHO grade I).

For ER and PR immunostaining, sections of formalin-fixed, paraffin-embedded tissue specimens were deparaffinized in xylene and processed through two changes of absolute ethanol. Sections were rehydrated through an ethanol series and briefly soaked on phosphate buffered saline. The endogenous peroxidase activity was blocked with 0.3% H_2O_2 for 10 min. Tissue sections were then microwaved as follows: slides were placed in a thermoresistant plastic jar with 10 mM citrate buffer and microwaved at high power (700 W) for 2 to 3 min until the solution came to boil. The oven was then reset at 55% power and heating was continued for 7-8 min to maintain gentle boil, with stops every 2 min to replace lost liquid.

Slides were then allowed to cool for 20-30 min in room temperature, and rinsed with several changes of distilled water before proceeding with the immunostaining. Nonspecific reactions were blocked with blocking reagents (Biotin Blocking System, DAKO Co., No.X0901). Tissue sections were then incubated with anti-progesterone monoclonal antibody (mouse anti-human progesterone receptor DAKO Co., No.1595) and anti-estrogen monoclonal antibody (mouse anti-human estrogen receptor DAKO Co., No.1575). The sections were incubated with biotin-labeled secondary antibody and avidin-biotin- peroxidase complex, one hour each step, with washing in PBS between steps.

All slides were determined by numbers of positively stained tumor cells nuclei in 10 high power fields. The ER and PR score was analyzed in relation to the patients' gender, age, localization and histological subtype of the meningiomas. The obtained data were statistically analyzed by the Mann-Whitney test. Sections of breast fibroadenoma were used as controls. Breast fibroadenoma stained for ER and PR acted as a positive control. For use as negative control, substitution of primary antibody with preimmune serum completely cancelled the immunostaining.

Results

The patient group consisted of 17 females and 13 males with a mean age of 48.7 years range 18-70 years. Based on the WHO criteria the histological subtyping of 30 meningiomas was as follows: 12 (40%) fibroblastic, 8 (26.67%) meningothelial, 3 (10%) transitional, 2 (6.67%) angiomatous, 2 (6.67%) psammomatous, 2 (6.67%) metaplastic and 1 (3.33%) secretory. Seven tumors were located in the parasagittal region, 6 in the falcial region, 8 in the anterior cranial fossa, 5 in the temporal region, 3 in the posterior cranial fossa and 1 in the occipital region.

All 30 (100%) tumor samples were ER-negative. Seventeen (57%) of all tumor samples were positive for PR. Positive immunostaining for PR was restricted to the tumor cells nuclei and no reaction was observed in the tumor cell cytoplasm, in the connective tissue and the endothelial cells (Figure 1).

PR were positive in 8 of 17 (47.50%) tumors in females and 9 of 13 (69.23%) tumors in males (Mann-Whitney, $p<0.05$; Figure 2).

The mean concentration of PR in the group of male patients was significantly higher ($p< 0.05$) than in the group of female patients. Age, tumor localization and histological subtype did not correlate with PR status.

Discussion

Usually meningiomas are considered to be benign and are associated with a relatively good prognosis [6, 13]. However, recurrence of meningiomas is not restricted to the aggressive type, because histologically benign meningiomas may also recur and

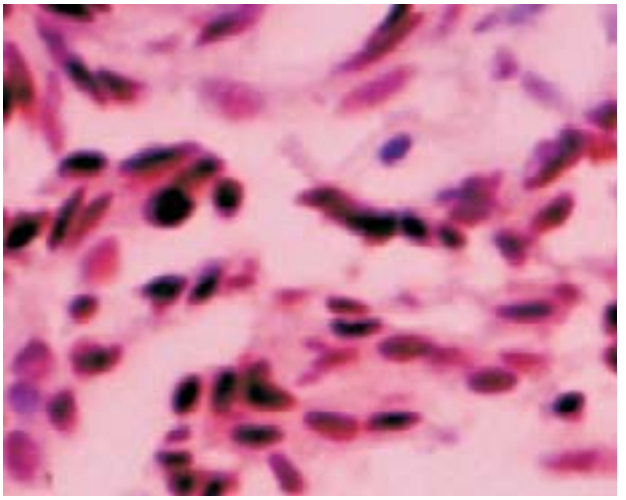

Figure 1. Tumor cell nuclei show positive staining for PR. Immunostaining for progesterone (x400).

have a 10-year regrowth rate of 15-20% [3-6, 13]. ER, PR and their participation in the growth of human meningiomas have been extensively analyzed in many recent studies [22-25]. The biological function of sex hormones in meningiomas and their molecular basis are still unknown.

ER and PR have not a clear role in meningiomas as in the case of breast carcinoma [26,27]. Despite variations in results, it is generally agreed that the majority of meningiomas possess PR but are devoid of ER [22]. We investigated the expression of ER and PR in 30 cases of benign, completely excised, meningiomas. In our study 56% of the tumor samples showed positive PR expression and we demonstrated a sex difference in the expression of PR: a statistically higher percentage of males with meningiomas show positive PR expression than females (69% *versus* 47.50, respectively; $p < 0.05$). Some studies have also found a positive correlation of high PR in male patients [28]. On the other hand, the majority of studies which analyzed malignant as well as atypical and benign meningiomas, showed that the expression of PR was higher in females [26].

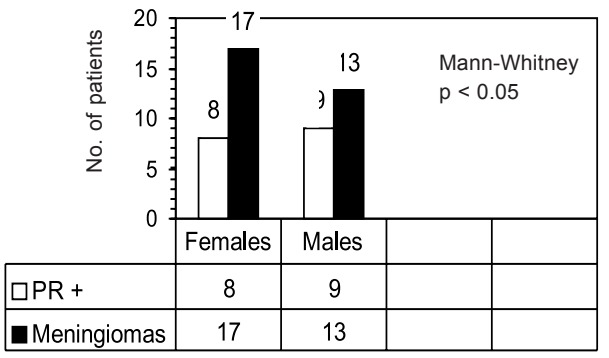

Figure 2. PR-positive nuclei of meningiomas in females and males patients

Our results agree with the relevant literature that patient age, localization and histological subtype of benign meningiomas do not correlate with PR status [23-25]. Although gender alone is not described as significant factor, our study established a significantly higher proportion ($p < 0.05$) of male patients with positive PR. This finding was also noticed by Brandis et al. [28].

In conclusion, our immunohistochemical study demonstrated complete absence of ER in 30 benign meningiomas. In contrast, PR were positive in 17 (57%) cases. Statistical analysis by the Mann-Whitney test showed that the mean concentration of PR in the group of male patients was higher ($p < 0.05$) than in the group of female patients.

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