Meningiomas - true dependent tumors?

KEYWORDS: Meningioma; Immunohistochemistry; Receptors, Estrogen; Receptors, Progesterone

ABSTRACT
Steroid hormones are involved in various aspects of growth, development, differentiation, and reproduction. The development of two major cancers breast and prostate is affected by hormones in the body, as well as some sarcomas. Although they do not arising from a tissue normally thought to be a target tissue for estrogen and progesterone, meningiomas show a number of epidemiological and clinical features which suggest that female sex hormones can play a role in their development. We investigated the sex hormone receptor content of benign meningiomas (WHO grade I), which is completely excited (Simpson graded I) by immunohistochemical methods. All of 30 (100%) tumor samples were estrogen negative. Seventeen (57%) of all tumor samples were positive for progesterone receptors. The mean concentration of progesterone receptors in the group of male patients was high (with \( p < 0.05 \)) as that in the group female patients. The present work offers data that may support the use of endocrine treatment for a recurrent or incompletely excised benign meningioma male patients.

INTRODUCTION
Pivotal experiments performed in the late 1950s and early 1960s, primarily in the laboratories of Gerald Mueller and Elwood Jensen. Jensen's laboratory showed that tritiated estradiol was specifically taken up and retained in the immature rat uterus, indicating the presence of an "estrogen-binding component" or "estrophilin," later termed "estrogen receptor" by Jensen (1,2). For Dr. Sanja Milenkoviæ, KBC Zemun, Dept. of Clinical Histopathology, 11080 Zemun, Vukova 9, Address correspondence to:

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nuclear localization signal and/or a transactivation domain. The E region is responsible for several functions, including ligand binding, heat shock protein (HSP) association, receptor dimerization, nuclear localization, hormone-dependent transactivation, and, in some cases, transcriptional repression. The F region is present in few receptors and exhibits minimal regulatory function (15).

In addition to the direct contact with the basal transcription machinery, nuclear receptors enhance or suppress transcription by recruiting an array of coactivators and corepressors, collectively named coregulators. Therefore, the mutation or aberrant expression of sex steroid receptor coregulators will affect the normal function of the sex steroid receptors and hence may participate in the development and progression of the cancers (16). The development of two major cancers breast and prostate is affected by hormones in the body, as well as some sarcomas.

The meninges develop from cells of the neural crest and mesenchyme (mesoderm), which migrate to surround the developing central nervous system (17,18). Although they do not arising from a tissue normally thought to be a target tissue for estrogen and progesterone, meningiomas show a number of epidemiological and clinical features which suggest that female sex hormones can play a role in their development. For example, higher incidence of meningiomas is in women and are rarely diagnosed before puberty or during the senium, corresponding to the time of maximal gonadal activity (19,20). Meningiomas have been documented clinically and radiologically to undergo relatively rapid expansion during pregnancy, followed by spontaneous regression postpartum (21-23). Some women suffer exacerbations of symptoms in the luteal phase of the menstrual cycle. These fluctuations in tumor size have been attributed to steroid-induced increased vascular engorgement of the tumor, or direct trophic effects of gonadal hormones on meningioma cells (24-26). Meningiomas are more common in obese women (26) and in patients with hormone-dependent breast carcinoma (27,28). The greater prevalence of these tumors in obese individuals may be related to higher circulating estrogen levels derived from the aromatization of androstenedione to estrone in adipocytes (29).

Numerous investigators have demonstrated the presence of PR and, to a lesser extent, ER in a significant number of human meningioma specimens (30). These observations suggest that progestins and possibly other gonadal steroids may directly modify the growth and differentiation of meningiomas. The presence of progesterin receptors may indicate a more favorable prognosis because progesterone receptor-negative meningiomas have been associated with a greater tendency for brain invasiveness, higher mitotic indices and necrosis and shorter disease-free intervals (31,32).

In an early study, the antiestrogen tamoxifen did not appreciably affect tumor size or neurological status in patients with inoperable meningiomas (33). On the other hand, the antiprogestin mifepristone (RU486) has been reported to induce stabilization or regression of meningiomas in a cohort of patients, suggesting that antiprogestin therapy may be useful in the management of these tumors (34). However, the effects of progestins and mifepristone on meningioma growth in vitro are contradictory (35-37).

The aim of our study was to investigate the sex hormone receptor content of benign meningiomas (WHO grade I), which is completely excided (Simpson gradus I) by immunohistochemical methods and evaluate possible relationship between receptor content and the gender and older patients, histological type of meningiomas and localization of tumors.

**MATERIAL AND METHODS**

Surgical specimens were obtained from thirty (30) consecutively treated patients with intracranial meningiomas operated in the Department of Neurosurgery CHC Zemun during the 2001/2002 year. Tissue samples of meningiomas were obtained from peripheral area of the tumors with nonheat-producing instruments, necrosis and bleeding. All of tumors operated in toto (Simpson gradus I). Tumor tissue was fixed in formalin and embedded in paraffin by standard methods. Section (5nm) were stained with Hematoxylin and Eosin, Periodic Acid Schiff and Gordon Sweett reticulin. Tumors were classified according to the new classification system of the WHO (World Health Organization), as a benign WHO grade I.

For progesterone and estrogen immunostaining, tissue sections of formalin fixed, paraffin embedded surgical 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% H2O2 for 10 minutes. Tissue sections were then microwaved as follows: slides were placed in a thermostable plastic jar with 10 mM citrate buffer and microwaved at high power (700W) for 203 minutes until the solution came to rapid boil. The oven was then reset at 55% power and heating was continued for 7-8 minutes to maintain gentle boil, with stops every 2 minutes to replace lost liquid. Slides were then allowed to cool for 20-30 minutes on the room temperature, and rinsed with several changes of distilled water before proceeding with the immunostaining. Nonspecific reaction were blocked by incubating the sections with blocking reagents (Biotin blocking System, DAKO Co. No.X0901). Tissue section were than 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 the avidin-biotin-peroxi-dase complex, one hour each step, with washing in PBS between steps. Sections of tissue fibroadenoma gill. mammae used as a positive and negative control.

All slides were determined by numbers positively stained tumor cells nuclei in the 10 high power fields (400X); The PR and ER score were analyzed against patients’ gender, age and histological subtype of the tumor. The correlation between number of positively nuclei and PR and ER status was determined by the analytic statistical test Mann Whitney.

**RESULTS AND DISCUSSION**

The patient group consisted of 13 men and 17 women with a mean age of 48.7 years (SD-standard error 13.5 years). Based on the WHO criteria intracranials meningiomas were classified as fibroblastic 12 (40%), meningotheelial 8 (26.67%), transitional 3 (10%), angiomatosus 2 (6.67%), psammomatous 2 (6.67%), atypical 2 (6.67%) and secretory types 1 (3.33%). Seven tumor were located in the parasagittal regions, 6 in the falcial regions, 5 in the basseos crani anterior, 5 in the regio temporalis, 3 in the basseos crani posterior, 3 in the regio frontalis and 1 in the regio occipitais. All of 30 (100%) tumor samples were estrogen negative. Seventeen (57%) of all tumor samples were positive for progesterone receptor (Figure 1). Positive staining for progesterone receptors was restricted to the tumor cell nuclei and no reaction was observed in the tumor cell cytoplasm, in connective tissue and endothelial cells.

We found that 8 of 17 (47.05%)tumors in women had progesterone receptors and 9 of 13 (69.23%) tumors in males had progesterone receptors.

![Figure 1. PR expression in benign meningiomas](image-url)
The mean concentration of progesterone receptors in the group of male patients was high (with p < 0.05) as that in the group female patients (Figure 2). We found that age, location of tumor and histological subtype did not correlate with PR status.

Brest fibroadenoma tissue that had been stained for either the PR or ER acted as a positive control and stained strong and unequivocal nuclear immunoreactivity. For use as a negative control, substitution of primary antibody with preimmune serum completely abolished the immunostaining.

In breast cancers, estrogen (ER) and progesterone (PR) receptors control tumor development and growth, they are markers of hormone dependence and tumor aggressiveness, and they are targets for treatments with antiestrogens, aromatase inhibitors and progestins. In hormone-dependent breast cancer, the tumor cells have estrogen receptors (ER positive tumors) and need estrogen to grow. Although progesterone had no effect on growth in the cancer, the tumor cells have estrogen receptors (ER positive tumors) and need estrogen to grow. Although progesterone had no effect on growth in the control transfectant, the hormone markedly inhibited DNA synthesis and cell growth. This growth inhibition was associated with an arrest of cells in the G0/G1 phase of the cell cycle (38). Absence of PR expression in primary breast cancer is associated with disease progression and may be a marker of an aggressive tumor phenotype (39). In ER+ tumors, the PR expression was significantly related to: age, menopausal status, tumor size, SBR grade, and histological type (40).

Tamoxifen and anti-estrogens like tamoxifen compete with estrogen for binding to estrogen receptors, thus blocking tumor growth stimulated by estrogen. However, with uterine tissue, the tamoxifen-receptor complex might stimulate endometrial and endometrial tumor growth (41). The new generation of potent steroidal and nonsteroidal inhibitors of the enzyme aromatase act by decreasing estrogen production throughout the body in postmenopausal women. Three new aromatase inhibitors are: anastrozole (ARIMIDEX) letrozole (FEMARA), and vorozole (RIVIZOR) (42-44).

Androgen plays a critical role in the promotion and growth of prostate cancer. Anti-hormonotherapy includes suppressing the release of male hormones using high doses of female hormones (estrogens), hormone-suppressing drugs, and anti-androgens to block androgen receptors. androgen induced blockade of caspase activation in both intrinsic and extrinsic cell death pathways and thereby was able to protect prostate cancer cells from androgen blocks apoptosis of hormone-dependent prostate cancer cells (45).

Liposarcomas (43%) and leiomyosarcomas (60%) had a high incidence of estrogen receptor. In contrast, sarcomas of fibrous and synovial tissue origin lacked any detectable receptor for estrogen. Malignant fibrous histiocytoma had the highest incidence of glucocorticoid (66%) and androgen (66%) receptors. The incidence of receptors for estrogen and glucocorticoid was higher in female than in male patients (62% and 30%, respectively) (46).

Usually meningiomas are considered to be benign and are associated with a relatively good prognosis (47,48). It has recently been established that atypical and anaplastic meningiomas exhibit an overall increased rate of recurrence, even after gross total resection. However, recurrence of meningiomas is not restricted to the aggressive type, because histologically benign meningiomas may also recur and have 10-year regrowth rate of 15%-20% (47-49). Estrogen receptors, progesterone receptors and their participation in the growth of human meningiomas have been extensively analyzed by many recent studies. However, there are numerous discrepancies in the literature among the results for estrogen receptor (ER), with some groups claiming estrogen receptors are present, while other groups have not found them (50-53). The biological function of sex hormones in meningiomas and their molecular basis are still unknown.

PR and ER have not a relationship in meningiomas as well as in case of the carcinoma glandulae mammae. Despite variations in results it is generally agreed that the majority of meningiomas possess the PR but devoid of the ER (50). We investigated the expression of PR and ER in 30 cases of benign completely exdices meningiomas. In our studies 56% of the 30 tumors samples showed PR expression. We demonstrated a sex difference in the expression of PR and the higher percentage of male with meningiomas have progesterone expression than the women. We found that 9 of 13 (69%) tumors in man had PR; in contrast only 8 of 17 (35%) tumors in women. Other studies have not found a positive correlation between male sex of patients, but some studies which analyzed malignant as well as atypical and benign meningiomas, showed that the expression PR was higher in women (54).

Our data are agreement with general consensus in the literature that patient age, localization of the tumor and histological subtype of the benign meningiomas do not correlate with PR status (51-53). Although gender alone was not a significant factor, there was in our studies, a higher proportion (p>0.05) male patients with positive PR. The presence of nuclear PR in tumor cells provides a benign form of tumors male patients.

**CONCLUSION**

The present work offers data that may support the use of endocrine treatment for a recidivism or incompletey excides benign meningiomas male patients.

**REFERENCES**


