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Assessing the Prognostic Importance of ER, PR Expression in Meningiomas by Comparing with Proliferative Rate Using Ki67

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Abstract

Background: Meningiomas are common brain tumors which are mostly benign and recur frequently. These tumors exhibit steroid hormone receptors which are related to the behavior of the tumor. *Aim*: To conduct a retrospective study to evaluate the presence of progesterone and estrogen receptors in meningiomas and to correlate their expression with expression of proliferative marker Ki67. *Materials and Methods*: 24 cases of meningiomas were studied immunohistochemically to detect the expression of ER,PR and Ki67. Other parameters like age and sex were also analyzed. *Results*: 24 Cases were analyzed and all of them were ER negative. 3 cases were strongly positive, 16 cases were moderately positive and 5 cases were weakly positive for PR immunoreactivity. 3 cases showed moderate positivity, 13 cases were weakly positive and 8 were negative for Ki67. 2 cases of atypical meningioma and 1 case of meningothelial meningioma showed moderate positivity with Ki67and weak positivity with PR immunostaining. Most of these tumors were in the age group of 40-50 years and were seen in females. *Conclusion*: Tumors with increased PR expression had decreased proliferative rate when compared to tumors with increased Ki67 and decreased PR expression indicating that PR expression is better prognostic marker for these tumors.

Keywords: Meningioma; Progesterone; Estrogen Receptors; Proliferative Marker Ki67.

Introduction

Meningioma is the commonest benign brain tumor arising from the arachnoid cells. They are divided into benign (90%), atypical and anaplastic (0.9% - 10.6%)[1]. 19% of meningiomas occur intracranially and 25% of them are seen in the spinal cord [2]. WHO Grading system distinguishes 3 grades of malignancy depending upon microscopic morphological features, which fails in predicting the clinical behavior as these tumors have variable growth potential.

Meningiomas harbor different quantities of progesterone, estrogen, glucocorticoids, androgen, prostaglandin, dopamine, prolactin and growth factor receptors. The presence of hormonal receptors would help for hormonal manipulation of tumors in patients with tumor recurrence, incomplete surgical resection and in unaccessible tumors. Though less number of cases showed estrogen receptors, but progesterone receptors and role of antiprogesterone therapy in meningioma have been studied in different works [3].

In our study we tried to evaluate the relationship between pathologic type of tumor with age, sex, presence or absence of progesterone and estrogen receptors and proliferation activity of the tumor cells by using ki67 marker.

Material and Methods

This retrospective study included 24 patients with meningiomas operated at the neurosurgical department, Narayana Medical College, Nellore between 2013 and 2016. All the specimens were sent to department of Pathology for histopathological examination.

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Out of 24 cases, 4 cases were male patients and 20 were female patients. Paraffin wax embedded tissue sections were stained by Hematoxylin and Eosin. Types of meningiomas were categorized depending upon the WHO classification. Immunohistochemical detection for estrogen and progesterone receptors was performed by using anti-ER and anti-PR monoclonal antibodies purchased from DAKO. Paraffin embedded sections were kept in xylene for deparaffinization and processed through ethanol. For reversing the effect of formalin fixation, tissue sections are microwaved in citrate buffer solution (pH 6.0). Tissue sections are treated with methanol containing 0.3% H_2O_2 for half an hour to block the endogenous peroxydase activity. Sections are rinsed with tris buffer solution and are incubated with normal horse serum to block the non-specific reactions. Sections are incubated with primary antibody. later they are incubated with secondary antibody and the avidin-biotin-peroxides after washing with tris buffer solution between steps. 3-3′ diaminobenzidine was used to visualize the antigen antibody bondage. The sections are counterstained with hematoxylin. Breast tissue was used as positive control for ER and PR.

All sections were examined for the receptor status regardless of tumor grade. Receptor status of tumor tissue was graded depending upon the percentage of positive tumor cell nuclei. They were graded as Grade 0 – when no tumor cells were positively stained, grade 1 (weekly positive) – less than 10% of tumor nuclei were positively stained, grade 2 (moderately positive) – 10-50% of tumor cell nuclei were positively stained and grade 3 (strongly stained) – more than 50% of the tumor cell nuclei were positive.

The tumor was categorized as atypical, when it has atleast two of the features described: high nuclear cytoplasmic ratio, hypercellularity, prominent nucleoli, brisk mitotic activity (5 mitotic figures/ 10hpf), presence of necrosis and invasion into the brain parenchyma. When tumor showed cytological anaplasia, brain invasion and many mitotic figures, it was considered as Anaplastic meningioma.

Results

Among 24 cases, 12 cases were of transitional meningiomas (50%), 9 cases were of fibroblastic memningioma (37.5%), 1 case of meningotheliomatous meningioma (4.17%) and 2cases of atypical meningioams (8.3 %) .

Out of 24 cases of meningiomas, 4 cases were in males and 20 cases were in females (Table 1). Maximum number of patients were in the age group of 40-50 years (Table2).

All the cases were negative for estrogen receptors. 3 cases were strongly positive, 15 cases were moderately positive and 7 cases were weakly positive for progesterone receptors. Only 2 cases of atypical meningiomas were moderately positive for ki67, 14 cases were weakly positive and 8 cases were negative for ki67 marker (Table 3).

In our study when the PR status was compared in relation to the age and sex, most of the patients who showed strong positivity with PR in tumor cells were in the age group of 40-50 years and were females. Out of 4 cases in males all were weakly positive for PR (Table 4).

Progesterone receptor staining was inversely related to the ki67 staining. 2 cases of atypical meningiomas which were weakly positive for PR receptors showed strong positivity with ki67 staining . 1 case of meningotheliomatous meningioma was weakly positive for PR receptor staining and was weakly positive for ki 67. 3 cases of strongly PR positive meningiomas were negative with ki 67, 9 moderately positive PR tumors were negative with ki 67 and remaining 9 cases were weakly positive for ki 67. (Table 5).

Table 1: Sex distribution of variants of meningiomas

Types of meningioma	Females (n=20)	Males (n=4)
Transitional meningioma	11 (45.83%)	1 (4.17%)
Fibroblastic meningioma (n=9)	9 (37.5%)	-
Meningotheliomatous meningioma (n=1)	-	1 (4.17%)
Atypical meningioma	-	2 (8.3%)

Table 2: Meningiomas in different age groups

Age group in years	Meningiomas (n=24)
30 – 40 yrs	-
40 – 50 yrs	18 (75%)
50 – 60 yrs	3 (12.5%)
60 yrs and above	3 (12.5%)

Table 3: Expression of ER, PR and Ki67 in different types of meningiomas

Receptor s	Fibroblastic meningioma	Transitional meningioma	Meningothelial meningioma	Atypical meningioma
ER	Negative	Negative	Negative	Negative
PR				
Weakly positive	-	3	1	2
Moderately positive	6	9		
Strongly positive	3			
Ki 67				
Weakly positive	6	7	1	-
Moderately positive	-	-	-	2
Strongly positive	-	-	-	-
Negative	3	5	-	-

Table 4: Expression of ER and PR and different sexes

Receptor	Females	Males
ER	Negative	Negative
PR		
Weakly positive	2	4
Moderately positive	15	
Strongly positive	3	

Table 5: Comparision of PR receptor expression with Ki67 expression

PR receptor status	Ki 67			
	Strongly positive	Moderately positive	Weakly positive	Negative
Strongly positive	-	-	-	3
Moderately positive	-	-	6	9
Weakly positive	-	2	3	-

Discussion

Meningiomas are well circumscribed, slowly growing tumors which are generally benign, though some of them show atypical and anaplastic features. Many studies have suggested that the growth of meningiomas are related to the female sex hormones. During the luteal phase of menstrual cycle and pregnancy, these tumors were observed to grow in size [4]. Surgical removal is the treatment for these tumors. However, few tumors are not operable because of their invasion into the adjacent brain parenchyma and bone or due to poor clinical condition of elderly patients [5]. Though the WHO grade I meningiomas were removed completely, they frequently recurred [6].

Donnel et al in 1979 first described the presence of hormonal receptors in the meningiomas . Receptor binding assays were used to detect the estrogen receptors (ER) and progesterone receptors (PR) [7]. In recent years, immunohistochemical techniques with monoclonal antibodies are used to detect the receptors which is reliable and rapid method for assessing receptor status. In addition this method also help to do retrospective study by utilizing stored tissue material and also detects receptors in small amount of tissue [8].

Majority of the studies has shown that most of the meningiomas were immunoreactive for PR and ER was not detectable in almost all of them which suggested that these were estrogen independent PR . The significance of these hormones in the growth of tumors is unclear. Studies done by Adams et al suggested that the growth of the meningiomas were not related to PR [9]. While Jay et al showed that growth of the meningiomas were modified by hormonal manipulation [10]. Some of the studies has shown that culture medium with progesterone increased the sensitivity of meningothelial tumor cells to mitogenic stimuli along with growth factors like epidermal growth factor, where as progesterone receptor blocking agents like mifepristone counteracts the effects of progesterone.

In our study most of the tumors were in females. But atypical meningiomas were noted in the male patients. There was no significant relation between the PR receptor expression and sex. However as our study included small number of male patients, we could not come to conclusion. Our study correlated with the study done by Fewing et al (2000), which showed that prevalence of malignant tumors was more in males and also no significant correlation was found between the sex and PR receptor status of tumor cells [11].

In our study progesterone receptors were expressed more in benign tumors than the atypical meningiomas. The tumors which were strongly positive for PR did not show ki67 positivity and tumors which were weakly positive for PR showed positivity with ki67. This indicated that the tumors with high proliferative activity showed low PR expression. Atypical meningiomas were weakly positive for PR receptors but showed ki67 positivity. This correlated with study done by Taghipour M et al [1]. Wahab et al reported that the tumors with positive progesterone receptors had less recurrence rate [12]. However studies done by Roser F et al suggested that only PR status cannot predict the prognosis in these tumors. The proliferative index should be used in combination with PR status to predict the prognosis of meningiomas [2].

Walter et al has shown that preoperative administration of medroxyprogesterone in patients with meningiomas that have positive PR receptors would show better clinical response when compared to patients who had tumor cells that were without PR receptors [13].

Though surgery is the treatment for the meningiomas, in some cases where tumor is not accessible to surgery or in elderly patients or in malignant tumors where complete removal is not possible due to invasion into the adjacent structures , antiprogesterone agents can be used in addition to radiotherapy.

Conclusion

The expression of PR status helps in evaluation of biological behavior of meningiomas. The tumors which showed increased expression of PR had decreased proliferation rate indicating better prognosis. Atypical tumors with increased proliferative rate showed decreased PR expression. Anti progesterone drugs can be used to decrease the recurrence rate after surgical removal of tumors.

References

1. M.Taghipour, SM Rakei, A Monabati, M Nahavandi-Nejad. The role of estrogen and progesterone receptors in grading of the malignancy of meningioma. Iranian Red Crescent Medical journal. 2007; 9(1):17-21.
2. Roser F, Nakamura M, Bellinzona M, Rosahl SK, Ostertag H, Samii M. The prognostic value of progesterone receptor status in meningiomas. J Clin Pathol. 2004; 57(10):1033-1037.
3. Fewings P E, Battersby RDE, Timperley WR. Long-term follow up of progesterone receptors status in benign meningioma: a prognostic indicator of recurrence? J Neurosurg 2000; 92:401-5.
4. Bickerstaff E R, Small JM, Guest IA. The relapsing course of certain meningiomas in relation to pregnancy and menstruation. J Neurol Neurosurg Psychiatry 1958; 21:89-91.
5. May PL, Broome JC, Path MRC et al. The prediction of recurrence in meningiomas. J Neurosurg 1989; 71:347-351.
6. Nakasu S, Nakasu Y, Matsuda M. Meningioma recurrence. J Neurosurg 2000; 92:897-9.
7. Cahill DW, Bashirelahi N, Solomon LW et al. Estrogen and Progesterone receptors in meningiomas. J Neurosurg 1984; 60:985-993.
8. Perrot-Applanat M, Groyer-Picard M T, Kujas M. Immunocytochemical study of progesterone receptors in human meningioma. Acta Neurochir (Wein) 1992; 115:20-30.
9. Adams EF, Schrell U, Honegger J et al. Effects of steroids and EGF on growth of meningiomas. Acta endocrinol 1989; 120:257-260.
10. Jay JR, MacLaughlin DT, Riley KR, Martuza R. Modulation of meningioma cell growth by sex steroid hormones invitro. J Neurosurg 1985; 62:757-762.
11. Fewing PE, Battersby RDE, Timperley WR. Long-term follow up of progesterone receptor status in benign meningiom: a prognostic indicator of recurrence? J Neurosurg 2000; 92:401-5.
12. Wahab M, Al Azzawi FN. Meningioma and hormonal influences. Climacteric 2003; 6:285-92.
13. Walter LM, Rogers PA, Girling JE. The role of progesterone in endometrial angiogenesis in pregnant and ovariectomised mice. Reproduction 2005; 29:765-77.