Original Research Article

Estrogen and progesterone receptor status in meningioma and its correlation with mib-1 labeling index

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A B S T R A C T

Introduction: Meningiomas are mostly benign tumour and major prognostic factor for recurrence is mostly dependent on the histopathological category, proliferation indices, grading and estrogen (ER) and progesterone (PR) receptor status. The present study was undertaken to find ER, PR receptor in excised specimen of meningioma and its correlation with Ki67 labelling index.

Materials and Methods: 75 cases of meningioma collected over period of 2 years was subjected to Haematoxylin and Eosin staining for routine histopathological investigation and immunohistochemical staining against PR, ER and Ki-67 by means of mouse monoclonal antibodies. Ki-67 labelling index was determined and Histological grade, PR, ER receptor status was evaluated.

Results: The Mean Ki-67 LI was significantly higher in PR-negative versus PR-positive meningioma, Grade II versus Grade I and males versus females. Whereas the PR positivity was significantly higher in Grade I versus Grade II and females versus males. A strong converse relationship was established between PR expression and Ki-67 LI.

Conclusions: As per the results it has been revealed that immnodetection of ki-67 LI and PR expressions in meningiomas are the important indicators for assessing prognosis and recurrence rate in meningioms.

1. Introduction

Meningiomas are hormone related, slowly growing CNS neoplasms, usually considered to be benign and resulting from meningiothelial cells. Meningiomas could be subcategorized as grade I, II and III based on the subtyping of the WHO. Even though, most of the tumors are benign and of WHO grade I; II (atypical) and III (anaplastic) lesions are not uncommon and demonstrate a greater affinity to metastasize or recur after treatment in comparison with those of grade I.[1,2]

The clinical outcome of meningiomas cannot always be predicted by histopathology alone; 2-3% of histologically benign meningiomas recur following macroscopically complete surgical removal, while some others present an exceptionally rapid growth in the absence of histological evidence of atypia.[3] However, meningiomas are considered as primarily benign tumours however, some meningiomas have aggressive characteristics with cerebral invasion, metastasis, and fatal outcome. Ki-67 and its formalin resistant MIB-1, both react with a nuclear antigen expressed by proliferating cells, thus providing a measurement for the growth fraction in individual tumors.[4].

Speculations that meningiomas are subject to gender specific hormone influence is supported by their higher incidence in females, their documented association with breast carcinomas in the same patients and reports of exacerbation of symptoms during pregnancy and the luteal phase of the menstrual cycle.[5] Hormone receptor status in meningiomas has been recognized as follows, despite frequent discrepancies in the literature. The level of ER has always been equivocal, ranging from low to almost untraceable by immunohistochemistry whereas a high levels of PR has high percentage of tumours display.[6]

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The prognostic role of ER and PR has been extensively discussed in different circumstances, predominantly in breast cancer,[7–9] in cases with hepatotoxicity,[10] some bacterial infections,[11] cancers in animals,[12] tongue carcinoma,[13] malignant and benign skin lesions[14] and lung malignancy[15]; the role of PR and ER is even more widespread for the status of Ki-67; such as t h e role of these factors in meningioma, however, is not fully understood and ongoing debate is still present in the literature.[16] [16]. Therefore the present study was undertaken to investigate the presence of ER and PR, and their relation to proliferative marker Ki-67.

2. Materials and Methods

This prospective non-randomized trial was conducted in 75 diagnosed cases of meningioma at Bangur Institute of Neurosciences (BIN) & S.S.K.M. Hospital Kolkata over a period of 2yrs from January 2014 to December 2015. All cases of meningioma diagnosed on radiological basis conformed on histopathology were included while patients not giving consent for operation and performance of receptor analysis were excluded. After the subject's guardian had been given a complete description of the study, written inform consents were obtained. The protocol was approved by ethical committee of IPGMER, SSKM Hospital Kolkata.

All the patients were resected at the initial operation. Resection was based on the surgeon's assessment at the time of surgery. Complete clinical record and data for cases, including the age at resection, sex, radiographic and discharge summaries, site of the tumour, was submitted by the respective neurosurgeon. The cases were operated in Bangur Institute of Neurosciences, Faculty of Neurosurgery, West Bengal University of Health Sciences, whereas the histopathological assessment to be done in Pathology Department, I.P.G.M.E.R, SSKM, West Bengal University of Health Sciences. Each paraffin block was re-cut by microtome at 5μ, section was stained with Haematoxylin and Eosin for regular histopathological investigation and immunohistochemical staining against ER, PR and Ki-67 using mouse monoclonal antibodies anti- estrogen, anti-progesterone and anti-Ki-67/MIB-1 antibodies was done. Parameters studied were ER, PR receptor status and Ki67 labelling index and relationship of receptor status with grade of tumour.

Statistical analysis

For analytical purposes the patients of meningioma with different age groups, gender, different grades and histopathological types were grouped according to PR, ER & Ki-67 staining and their correlations were found with multiple linear regression and Pearson coefficient correlation with SPSS version.[16]

3. Results

Total 75 cases of meningioma were studied with age range of 21 years to 70 years; It was found that there is increase in incidence in middle age with maximum incidence in 41- 50 years. There were 25 male and 50 female patients. As per the location, 70(93.33%) were cranial and 5 cases (6.67%) were spinal meningioma. According to histological type, meningothelial meningioma among 75 meningioma patients were 30 (40%), those having histopathology report of trasitional were 25 (33.33%), patients having Fibrous histopathology were 4 (5.33%), secretory histopathology was in 5 cases (6.66%), angioblastic in 3 (4%), psammomatous in 2 (2.66%) cases., and there were no cases of microcystic, lymphoplasmacyte rich and metaplastic meningioma in our series.

The patient were graded as per the WHO 2007 grading system, in grade I there were 69 patients (92%), grade II meningioma were 5 (6.67%). and, in grade III meningioma was 1(1.33%) patients.

Among 75 cases of meningioma 50 (66.67%) cases were positive for PR and negative for ER. 15 (20%) cases were negative for both PR and ER, 5 (6.67%) cases were positive for both PR and ER, and 5 (6.66%) cases were negative for PR but positive for ER

The total number of cases positive for PR were 55(73.33%) and all were WHO grade 1 meningioma, and total cases positive for estrogen receptors were 10 (13.33%). Figure 1

Out of 50 female patients, 45 (90%) patients were positive for PR, and out of 25 male patients, 10 (40%) patients were positive for PR showing association of progesterone receptor positivity with female gender.(p<0.001).
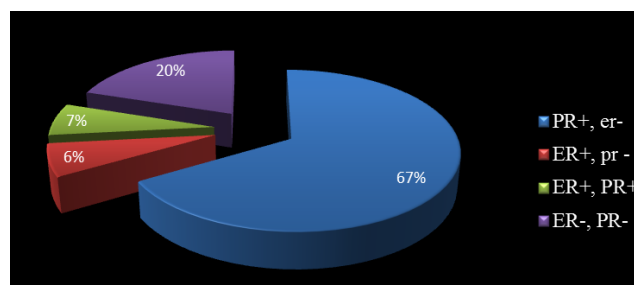

Fig. 1: Estrogen and Progesteron Receptor Status

Progesterone receptor was found positive in 55 cases (77.46%) primary meningioma out of 71 cases and all 4 cases of recurrent meningioma were negative for progesterone receptor. It indicates that primary meningiomas are more associated with PR positive (p<0.001).

Among 75 cases of meningioma, 64 patients (85.33%) were having Ki 67 labeling index below range of 1-4% which were largely grade1, 10 patients (13.33%) were having Ki-67 Li in the range of 5-10% which were mainly

grade2, only 1 patient had Ki 67 Li of 14% which was grad 3 tumour.

Mean Ki -67 Labelling index in 55 cases of progesterone positive meningioma was 1.13%, compared to 3.75% mean Ki 67 labeling index in progesterone negative meningioma, (Table 1), indicating higher mitosis and proliferation in progesterone receptor negative meningioma (Pearson coefficient-5.77,p value<0.001).

Table 1: Correlation between progesterone receptors status and Ki-67 labeling index

Progesteron receptor status	Positive(55 Patients)	Negative (25 Patients)
Mean Ki 67 labeling index	1.13%	3.75%

We determined Ki-67 LIs of all the 75 cases Mean Ki 67 labeling index in male was 2.4% which was much more than mean Ki 67 labeling in Female patients 1.54%, (Pearson coefficient-5.33,p value<0.001).

4. Discussion

Several scientific studies have been carried out till date to investigate the role of Ki-67 and PR, ER in meningioma and also to evaluate their significance in predicting the behaviour of meningioma as prognostic factors. On the other hand the different studies had given varied propositions regarding the correlation of PR and Ki-67, ER expression with the biological behaviour of meningioma. Histopathologically in present series out of 75 cases, 30 (40%) were meningothelial, 25(33.33%) transitional, 5(6.66%) secretory, 4(5.33%) fibrous, 2 (2.66%) psammomatous, three (4%) were angiomatous, and there were 2 cases of atypical and clear cell meningioma each (2.66% each), and one (1.33%) case of chordoid and one (1.33%) case of papillary meningioma. These results are similar with that of Gursan et al study.[17] Our results differ from Mukh erjee et al[18] in which there is similar percentage of meningiothelial meningioma (36.7%) but lower percentage of trasitional meningioma (13.4%) and higher percentage of fibrous meningioma (21.6%).

As per histological grade, the present study found that 69 (92%) cases of Grade I meningioma, 5 (6.66%) cases of atypical meningiomas i.e. Grade II and only 1 (1.33%) case of anaplastic meningioma i.e. Grade III. Similar to Mukherjee et al[18] and Nagashima et al[19], the present study constituted 8% of total cases of atypical and anaplastic meningiomas. The mean Ki-67 LIs was found significantly higher in male patients (2.4%) than female patients (1.5%) like the study done by Mukherjee et al[18] Matsuno et al.[20]. This gender difference revealed the greater incidence of non-benign meningioma in males.

Ki-67 LIs of 75 meningiomas ranging between 1 to 14% which is coincide with the findings of Nagashima et al[19]

that is 0.4 to 16.4%. Likewise Ki-67 LIs found significantly higher in Grade II meningioma than Grade I as reported in previous studies.[21,22]. The statistically significant difference was observed in Ki-67 LIs in recurrent and non-recurrent meningiomas which resemble with the results of Matsuno et al[20], Abramovich et al[21] and Miyagami et al[23]. In non-recurrent tumors, the mean Ki-67 LI was 1.56% whereas recurrent tumors showed LI of 7.25% which correlated with the previous studies.[18,23]

The PR positivity in present study was found to be 73.33% of total cases and similar percentage was found with the study done by Mukherjee et al[18] and other authors.[17,19,22] The PR immunostaining was more abundant in female that is 90% in females and 40% in males which revealed statistically significant gender-related difference. In support of this, the previous studies[17,18,24,25] also demonstrated a significant gender difference in the expression of the PR which is attributed due to incidence of atypical and anaplastic meningomas in male patients. Although most of the studies show ed similar observation in terms of PR positivity in female patients while in male patients it largely differs and found 55-58% PR positivity.[17,25] The current study found PR expression was more frequently in meningothelial and transitional subtypes than in the fibroblastic histological type which resemble the earlier studies.[17,18,26]

In Grade I meningiomas, t he positive immunostaining rate for PR was significantly higher than in high-grade tumors which is like prior studies.[17–19] The present study revealed 79.71% PR positivity in Grade I meningiomas however Gursan et al[17] and Mukherjee et al[18] showed 76% and 70% positivity in the same grade respectively. We found that 100% recurrent meningiomas were PR-negative and similar to Fewings et al[27] while it was 80% in study by Mukherjee et al[18] there is a significant association between PR negativity and tumor recurrence.

There was a "strong" converse relationship between Ki-67 LI and PR expression. This was evident from the Ki-67 LIs were significantly higher in the PR-negative meningiomas than in the PR-positive tumors and t his outcome is supported by some other studies.[17–19,27] This was more evident in case of Grade I meningiomas and also in non-recurrent tumors, however six out of six high-grade meningiomas reveal ed PR negativity and high mean Ki-67 LI (6.50%). This effect is relatively analogous to Gursan et al[17] and Nagashima et al[19] found negative PR staining and high Ki-67 LI (6.50% to 7.37%) in high-grade meningiomas.

Hence, in addition to H and E staining, combining Ki-67 LI and PR expression can help not only in distinguishing between grades of meningiomas but also can help to pick which cases within the group of Grade I meningiomas are likely to recur.

5. Conclusion

The Results revealed that immnodetection of PR and ki-67 LI expressions in meningiomas are the important indicators for assessing prognosis and recurrence rate in meningioms.

6. Conflict of Interest

None

7. Source of Funding

None

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