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Research Paper

Progesterone Receptorexpression &its correlation with clinical, WHO Grade and Ki67 MIB1 proliferation index of meningioma: an institutional experience

Dr. Samrendra Kumar Singh[1], Dr. Dhananjay Kumar[2], Dr. O.P. Gupta[3] , Dr. Brajesh Kumar [3], Dr. Niraj Kanaujia [3] , Dr. K.M. Jha[4], Dr. Bipin Kumar[5]

1. *Associate Professor, Department of Neurosurgery, IGIMS, Patna*
2. *M.Ch. Trainee, Department of Neurosurgery, IGIMS, Patna*
3. *Assistant Professor, Department of Neurosurgery, IGIMS, Patna*
4. *Professor & Head of Department, Department of Neurosurgery, IGIMS, Patna*
5. *Professor & Head of Department, Department of Pathology, IGIMS, Patna*

Background: *The variable expression of progesterone receptor (PR) is noted in most cases of meningiomas and was found to have its own prognostic significance. However, its correlationwith patient clinical presentation, WHO grade of meningioma and ki67 MIB1 expression recurrence, has discussed in very few studies.*
Methods: *A prospective study in 53 cases of meningioma who underwent surgical resection done. The PR expression was graded as:* ***Grade 0****: no PR expression;* ***Grade 1:*** *low expression (<15%);* ***Grade 2:*** *moderately low (16–50%);* ***Grade 3:****moderately high (51–79%);* ***Grade 4:****High expression (≥80%). The PR values were correlated with the patientage and sex, WHO grade, and Ki-67 MIB1.*
Results:*There was no sex difference in PR expression grades in males and females (including premenopausal vs. postmenopausal women). The PR expression has shown low grade expression in the elderly group(p = 0.032) and there was an inverse correlation noted with WHO grade and Ki67-MIB1 (p <0.0001).*
Conclusion: *The lack of difference of PR expression betweenMales and Females, among females lack of differences in premenopausal and postmenopausal females and an inverse correlation of PR expression with WHO grade and Ki67-MIB1 are the most relevant unreported findings of this study.*
Keywords:*meningioma, Progesterone receptor(PR), WHO grade, proliferation index Ki 67 MIB1.*

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I. INTRODUCTION

Many clinical researches suggests that sex steroids play an important role in the growth of Meningiomas; these include the female predominance (F:M ratio 2:1),the reported rapid growth during pregnancy[1,2] and females who receive oralcontraceptives or hormone replacement therapy.[3,4] The expression of progesterone receptor (PR) is variable, some studies noted very high rate of expression (39-88%), whereas the expression of estrogen receptor (ER) is lower (<10%) and often undetectable.[5-7] The PR expression was found to be correlated with the WHO grade and meningioma proliferation rate.[8-11]

In this prospective study we will review Progesterone Receptor expression & its correlation with clinical, WHO Grade and Ki67 MIB1 proliferation index of meningioma.

II. MATERIALS AND METHODS:

Prospective study done in 53 patients admitted and operated between October 2019 to December 2021, in department of Neurosurgery, IGIMS, Patna

An ethical committee approval was taken from institutional ethical committee. The factors analyzed in the study included patient age and sex, WHO grade of meningioma, PR expression, and Ki67 MIB-1 proliferative index.

Age wise patients divided in two main groups: Group I or elderly ≥60 years old and Group II <60years. For the evaluation of sex, the female patients were divided intwo groups: Group A: premenopausal and GroupB: postmenopausal.

The surgical specimens were reviewed by pathologists in department of Pathology, IGIMS, Patna. The WHO grade was defined according to the 2007 WHO classification.[12] The immunohistochemical studies were performed to evaluatethe Ki67 MIB-1 and the PR expression.

The specimens were fixedin neutral buffered 10% formalin, embedded in paraffin, and cut into sections.The expression of PR was determined in all specimens. The quantitative evaluation wasexpressed as percentage for positive nuclei among 100 cells,for a total of 500 cells. The percentage of PR positivity wasdetermined by a semiquantitative scoring scale with respectto staining intensity, according to the recommendations for immunohistochemistry of hormonal receptors.[13]

The PR expression was graded as: **Grade 0**: no PR expression; **Grade 1:** low expression (<15%); **Grade 2:** moderately low (16–50%); **Grade 3:** moderately high (51–79%); **Grade 4:** High expression (≥80%).

The expression of Ki67 MIB-1 was evaluated in all specimens by using the monoclonal antibody MIB-1. Ki67-LI countwas performed by eye counting, taking the average on fiveadjacent representative fields of neoplastic cells in a hot spotarea. The values of Ki67-LI were classified into two groups: groupI ≤4%; group II >4%.

The histological types of WHO grade I meningiomas wereclassified as: meningothelial, transitional, fibroblastic,psammomatous, microcystic, angiomatous, and chordoid.The variables analyzed includes the patient age and sex, PRexpression, WHO grade, Ki67 Li.

III. RESULTS:

Outof 53 patients of meningioma , the PR expression grade was low (0–15%) in 9 (17%), moderately low (16–50%) in 12 (22.64%), moderately high in 11(20.8%) and high (≥80%) in 21 (39.62%). No cases with complete absence of PR expression were found. The data of the PRexpression analyzed as follows:

Patient Age and Sex:

The patients were 31 females (58.5%) and 22 males (41.5%); their agewas <60 years in 45 (84.9%) and ≥60 years in 8 (15.1%). The correlation of PR expression and Age of the patients (Table 1) has shown that high grade of PR expression (>80%) is more among younger age groups patients compared to elderly age groups.

The correlations between PR expressions and Sex of patients shows, there was no significant differences of PR expressions among females and males (Table 2). We also found no significant differences in PR expressions among premenopausal and postmenopausal Females(Table 2).

Table 1: PR expression and patients Age

PR expression	No. Of cases	>60 yrs	<60 yrs
L (0-15%)	9	3	6
ML (16-50%)	12	2	10
MH(51-79%)	11	2	9
H (>80%)	21	1	20

Table 2: PR expressions and patients sex

PR expression	Female	Premenop-ausal	Postmenop-ausal	Male
L (0-15%)	5	2	3	4
ML (16-50%)	5	2	3	7
MH(51-79%)	7	3	4	4
H (>80%)	14	4	10	7

PR Expression, WHO Grade, Ki67 MIB-1and Histological Type:

WHO grade II (atypical) meningiomas have shown high (≥80%) grade PR expression only in 4.7% of cases ; while WHO grade I tumours showed high grade PR expression in 95.3% of cases. This correlation was statistically significant ($p < 0.0005$) (Table 3).

The correlation between PR expression and proliferation rate (Ki67 LI) of meningiomas shown significant differences. Meningiomas with Ki67 LI >7% showed high grade (≥80%) PR expression only in 9.5% of cases (p =

PR expresion	**N. of cases**	Ki67 LI <7%	Ki67 LI >7%
L (0-15%)	9	4	5
ML (16-50%)	12	9	3
MH (51-79%)	11	9	2
H (>80%)	21	19	2

0.0023) while meningiomas with Ki67 LI<7% showed high grade (≥80%) PR expression in 90.5% of cases. (Table 4).
Thus, the study showing an inverse correlation of the PR expression with both the WHO grade and Ki67 LI.

Table 3: PR expression and WHO Grade of Meningiomas

PR expresion	**N. of cases**	**WHO Gr. I**	**WHO Gr. II**
L (0-15%)	9	5	4
ML (16-50%)	12	10	2
MH (51-79%)	11	10	1
H (>80%)	21	20	1

Table 4: PR expression and ki67 MIB1 of Meningiomas

The frequent histological type of WHO I meningiomas was transitional (32.1%) followed by meningothelial (22.6%). Tumours of psammomatous and angiomatous types showed slightly higher rates of high PR (>80%) expression (60% and 50% respectively) than transitional (47.1%) and fibroblastic (40%), but with no statistical significance (Table 5)

Table 5: PR expression and histological type of grade I meningiomas.

PR expresion	Meningothelial	Transitional	Psammomatous	Fibroblastic	Microcystic	Angiomatous
L (0-15%)	1	1	1	1	0	1
ML (16-50%)	2	5	1	1	1	0
MH (51-79%)	5	3	0	1	0	1
H (>80%)	4	8	3	2	1	2
Total	12	17	5	5	2	4

IV. DISCUSSION

The histopathology of meningiomas and PR expressions with its possible prognostic implications have been discussed in several studies.[14-21]

Definition of the Progesterone Receptor Expression

The cut-off values of Progesterone Receptor expression have variably values in different studies. Many studies report only negative or positive expression.[8,10,21] While others consider as positive only those cases with strong staining in >10% or moderate staining in >50%.[16,19]

In our study we used the semiquantitative scoring scalerecommended by the Group for Evaluation of PrognosticFactors using Immunohistochemistry, published in 1999;[13] we also slightly modified the cut-off of the lower expression (15%instead of 10%). The stratification of the data made for all cases with different positivity.

Progesterone Receptor Expression and Patient Age and Sex:

The correlationsbetween, PR expression of meningiomas and the different age groups is done only in very few studies. In our study we have found significantly higher rate ofPR expression ≥80% in patients aged <60 years, whereas lower PR values were not correlated. The results matcheswith those of Wolfsberger et al.[22] On the other hand, Roseret al,[23]Korhonen Ket al,[24] and Taghipour Met al,[25] did not findsignificant differences between younger and older patients. The differencesbetween our and these studies may bedue to thelesser stratification of the PR values.

According to our study, no significant difference was found between females and males in PR expression. While significant correlation between PR expression and patientsex was evidenced in four reviewed studies.[16,25,26,27,]

And others report slightly higher rate of expression in females or in males but with no statistical significance or norelevant sex difference, as in ourstudy.[14,24,28,]

All previous study have considered the overall female group without premenopausal or postmenopausal relationship to PR expression. We tried to find, if there any differences in PR expression among pre or post menopausal females but there were no significant differences of PR expression between premenopausaland postmenopausal females. This probably show that the PRexpression of meningiomas does not reflect the patienthormonal status.

Progesterone Receptor Expression and Histo-pathological Findings:

About the correlation between PR expression and histo-pathological findingsof meningiomas hasbeen discussed in many series, but the results are controversial. Some series found significantly higher rate of cases withhigh PR expression in benign WHO I meningiomas and low expression in atypical WHO II meningiomas.[6,9,10,16,25,27]

Aboutthe correlation between PR expression and Ki67 LI was also studied many series; some found significantly lower PR expression in meningiomas with higher Ki67-LI;[9,16,27] while others did not find significant differences.[15,18,21,]

Among the histological subtypes of WHO I meningiomas and PR expression were also studied. Some studiesfound significantly higher PR expression in the meningothelial meningioma, with no significant correlations with the other subtypes.[9,22,29,30]

In our study we found an inverse correlation of the PR expression with both the WHO grade and Ki67 LI, and the difference of PR expression between the histological subtypes of WHO grade I Meningiomas was not significant.

V. CONCLUSION:

The higher PR expression among younger age groups (<60 yrs.),the lack ofdifference of PR expression between premenopausal andpostmenopausal females, an inverse correlation of the PR expression with both the WHO grade and Ki67 MIB-1, and the no significant difference of PR expression between the histological subtypes of WHO grade I Meningiomas were the main findings of this study.

The immunohistochemical evaluation of the PR expressionshould be included in the routine histological study ofmeningiomas, together with the WHO grade and Ki67 LI.

The well-defined correlation of the PR status with the WHOgradeand Ki67 LI, is of prognostic significance. Foratypical WHO grade II intracranial meningiomas, the low PRexpression is a further risk factor of recurrence with the Ki67 LI.

Even WHO grade I meningiomas, without high Ki67-LI, thelow values of PR expression must suggest a closer follow-up

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