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Original Research Article

Study of epidemiological aspects and hormone receptor status of meningiomas

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ABSTRACT

Background: Meningiomas account for about a third of all central nervous system tumours worldwide. Though very common, quite less is known about its epidemiology. This study aims to establish the epidemiological parameters and hormone receptor status (Progesterone Receptor-PR) involved in the development of Meningiomas.
Methods: This observational study included 50 patients. Epidemiological parameters studied included age, sex, symptoms, history of hormone intake, smoking, recurrence, family history, history of other hormone related tumours and radiological assessment of tumour site. Surgical samples were grossed and typed according to the WHO standards. Immunohistochemical staining was done using PR to establish the role of hormonal receptors in the development of meningiomas.
Results: The mean age was 46.84±13.54 years. The ratio of male and female (Male:Female) was 1.0:2.3. 48.5% of females had history of hormonal pill intake and 28.6% had hormone related tumours, of which fibroid was most common. Amongst the sites involved cerebral convexity was most common (56%). Chi-square (χ^2) test showed that there was a significant association between histological grade and PR expression of the patients (p=0.0002).
Conclusions: Positivity for hormone receptors like PR, increased intake of hormonal pills by females and association of meningioma with hormone related tumours indicates that hormonal milieu plays a significant role in the growth of meningiomas$\chi\chi$. This could thus provide an insight to the pathogenesis of meningiomas. In addition, mifepristone, an anti-progestin could be a player in the medical management of meningiomas.

Keywords: Female, Meningioma, Progesterone receptor

INTRODUCTION

Meningiomas account for approximately 33.8% of all central nervous system tumours worldwide, while in India despite the lower number of registered cases, several hospital based cancer registries have shown that meningiomas are the most common primary intracranial tumours accounting for about 23.2% of all intracranial neoplasms amongst the adult population.[1,2] Though meningiomas are very common yet its epidemiological parameters have been studied less frequently compared to other brain tumours like gliomas. Hospital based tumour registries in India have also revealed that meningiomas are twice as common in females as compared to the males.[2] Further, the increased incidence of meningioma amongst the females in the reproductive age group has furthermore prompted a role of hormone receptors in the development of meningiomas.[3]

Of the several hormone receptors, we aim to study the role of Progesterone receptor (PR) and correlate it with the grades and subtypes of meningiomas. In addition, we

also aim at studying the several epidemiological parameters associated with the development of meningiomas.

METHODS

This observational study spanned from February 2016 to December 2019 and included 50 patients of both primary and recurrent meningiomas. The patients underwent neurosurgical interventions at Nil Ratan Sircar Medical college and hospital, Kolkata. Informed consent was taken from all the patients included in the study, according to ICMR (Indian Council of Medical Research) guidelines. Epidemiological parameters studied were age, sex, symptoms, history of hormonal pill intake, smoking, family history, history of other hormone related tumours, site of the tumour (determined radiologically) and history of tumour recurrence. Questionaires were prepared for providing the adequate history of the patients. Neurosurgical samples of the patients were grossed and histological tumour grading and subtyping was done according to the WHO standards. Immunohistochemical staining was further done using Monoclonal Mouse Antihuman PR Antibody to establish the role of hormonal receptors in the development of meningiomas. PR expression was further correlated with the histological grade and tumour subtypes. Breast tissue was used as a positive control for PR immunohistochemistry. The PR status was ascertained by a scoring scale with respect to intensity and proportion scores, Immuno Reactive Scores (IRS) were obtained by multiplying intensity score with proportion score similar to that used by Roser et al.[4] Intensity scoring was done as: 0- absent ; 1- weak; 2- moderate; and 3- strong while proportion scoring was done as : 0- absence of positive nuclei; 1- the presence of <10% positive tumor nuclei; 2- 10-50% positive tumour nuclei; 3- 51-80% positive tumour nuclei; and 4- >80% positive tumor nuclei. IRS ranged from 0 to 12. Tumors with IRS of 2 or more were considered as PR positive.[4]

RESULTS

Statistical Analysis was performed with the help of Epi Info (TM) 3.5.3. EPI INFO is a trademark of the Centers for Disease Control and Prevention (CDC). Descriptive statistical analyses were performed to calculate the mean with corresponding standard deviations (SD). Test of proportion was used to find the Standard Normal Deviate (Z) to compare the different proportions and Chi-square (χ^2) test was performed to find the associations. In the cases where one of the cell frequencies were less than 5 corrected Chi-square (χ^2) was used to find the association between variables. t-test was used to compare the means. Odds Ratio (OR) was calculated to find the risk factors with 96% confidence interval. A $p \leq 0.05$ was taken to be statistically significant.

The mean age (mean±SD) of the patients was 46.84±13.54 years. Only 2.0% of the patients were in the age group <15 years whereas 16% of the cases belonged to the age group of >60 yrs (Figure 1).

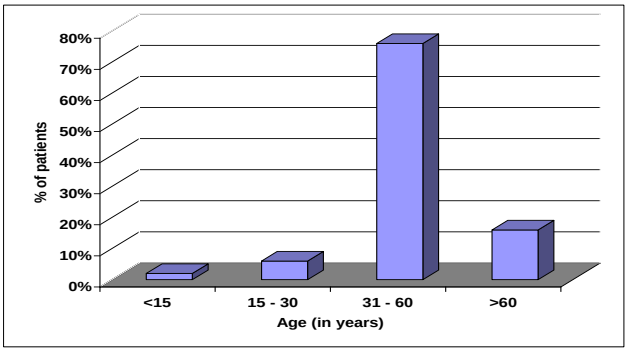

Figure 1: The age distribution of patients.

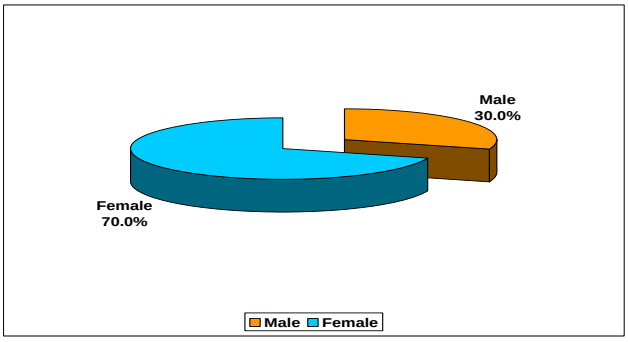

Figure 2: The gender distribution of the patients.

The ratio of male and female (Male:Female) was 1.0:2.3. Proportion of females was significantly higher than that of males (Z= 5.65; p<0.001) (Figure 2). The mean age (mean±SD) of males was 52.46±11.45 years with a range of 38-77. The mean age (mean±SD) of females was 44.42±13.79 years with a range of 8-72 years. Thus females were prone to have meningiomas at a younger age as compared to males. Early morning headache was the most common symptom (48%) followed by focal neurological deficit (22%). Amongst the females, 48.5% had history of hormone intake (Oral contraceptive Pill/Hormone replacement therapy). 40.0% of the patients (males and females) had a history of smoking. Of the total number of cases assessed 16% had a familial history of meningioma whereas 20.0% of the patients had a previous history of meningioma. Amongst the sites involved cerebral convexity was most common (56%) followed by parasagittal (12%) and spinal locations (12%). Only 11 (28.6%) had any other associated hormone related tumours out of which uterine fibroid was most common (20.0%).

WHO grading revealed that 43 out of 50 were WHO grade I meningiomas. Histopathologically WHO grade-I Meningiomas were significantly higher than other WHO grades (Z=10.75; p<0.0001) (Figure 3). Most of the cases (86%) were PR positive with an IRS of > or = 2 (Z=10.18; p<0.001). The mean (±SD) of the

immunoreactive scoring for PR was 7.56±4.43 with range 0.0 - 12.0 and the median was 8.0. Corrected Chi-square (χ^2) test showed that there was significant association between female gender and PR expression of the patients (p=0.0005) (Table 1).

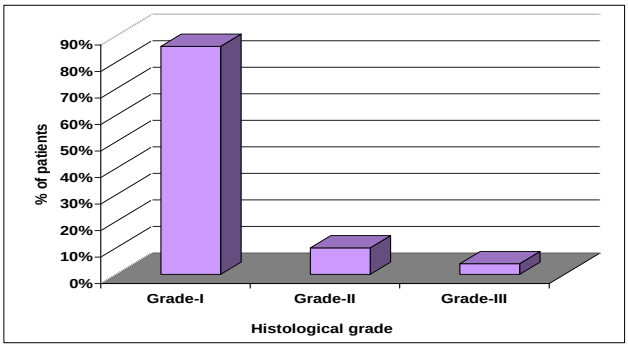

Figure 3: Histological grading of meningioma (WHO grade).

Table 1: Gender and PR expression of the patients.

Gender	PR expression		Total
	Positive	Negative	
Female	34	1	35
Row %	97.1	2.9	100.0
Col %	79.1	14.3	70.0
Male	9	6	15
Row %	60.0	40.0	100.0
Col %	20.9	85.7	30.0
Total	43	7	50
Row %	86.0	14.0	100.0
Col %	100.0	100.0	100.0

Table 2: Histological Grade and PR expression of the patients.

Histological grade	PR expression		Total
	Positive	Negative	
Grade I	43	0	43
Grade II	0	5	5
Grade III	0	2	2
Total	43	7	50

$\chi 2$=16.85; p=0.0002

Positive PR expression was 22.66 times more for female patients as compared to male patients and this was statistically significant [OR-22.66 (2.41, 213.11);p=0.0005]. Positive PR expression was 2.48 times more for the patients with age<50 years as compared to the patients with age≥50 years. Amongst the recurrent cases most were PR positive (90.0%) and the results were statistically significant (Z=11.31;p<0.001). Chi-square (χ^2) test showed that there was a significant association between histological grade and PR expression (Table 2) of the patients (=16.85; p=0.0002) in addition, corrected Chi-square (χ^2) test showed that there was also a significant association between histological subtype and PR expression of the patients (=50.00;p<0.0001). Of all the subtypes that were positive for PR. Meningothelial meningioma (Figure 4) was most common (38%) followed by Transitional meningioma (28%) (Figure 5).

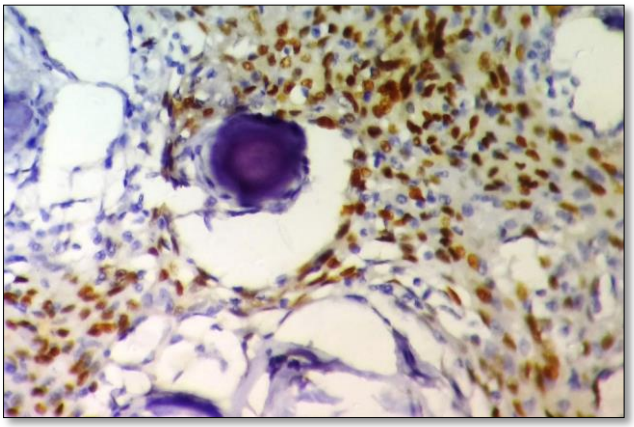

Figure 4: Meningothelial Meningioma (WHO grade I), PR immunostain, 400X.

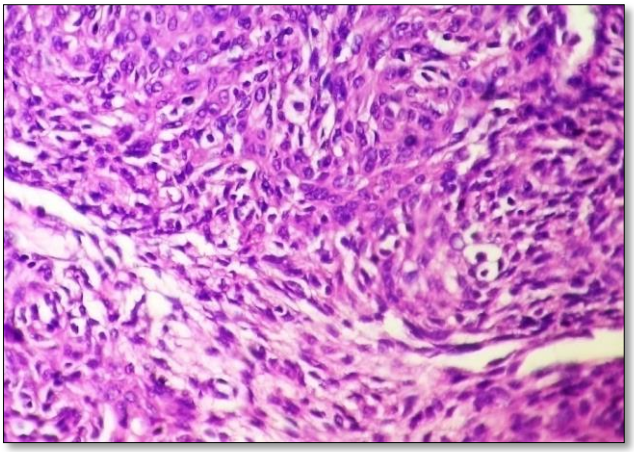

Figure 5: Transitional meningioma (WHO grade I), H&E, 400X.

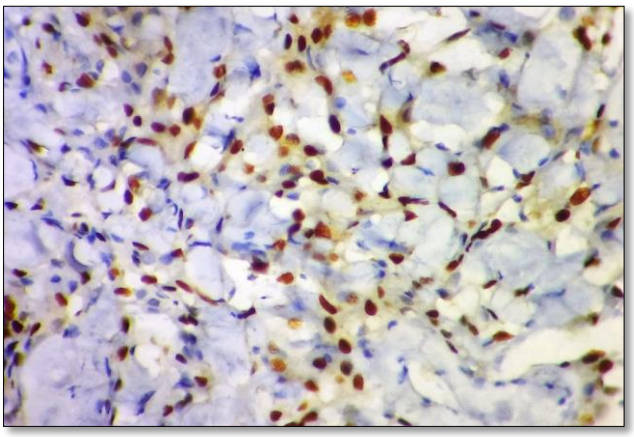

Figure 6: Micocystic meningioma (WHO grade I), PR immunostain, 400X.

However, Fibroblastic meningioma (8%), Angiomatous meningioma (6%), Psammomatous (4%) and Microcystic meningioma (2%) (Figure 6) were also PR positive.

DISCUSSION

Meningiomas are the most common benign intracranial, dural based tumours of the central nervous system, however its epidemiological parameters have less frequently been studied by the researchers as compared to other brain tumours. In addition its frequency is gender dependant being higher in the female population as compared to the males. Several studies in the past have also suggested similar findings however our study in addition to studying the epidemiological parameters also establishes the role of hormone receptors in the pathogenesis of meningioma, thus clearly indicating the biased attitude of the tumour towards the females as compared to the males.

The study was conducted over a span of 3 years and 10 months and included 50 patients of both primary and recurrent meningiomas. The mean age of the patients was 46.84±13.54 years whereas that of the females was 44.42±13.79 years. Similar findings were also elaborated by Johnson et al however, they found that age ranged between 65.0–84.6 years while in our study the age range was between 8-72 years.[5] In addition we also found that the males had a mean age group of 52.46±11.45 years with a range of 38-77 years whereas Magill et al who studied 1113 patients of meningioma found that the mean age of the patients (both male and female) was 55.7 years and the age range was between 8-90 years.[6] Our findings thus showed that females were affected by meningioma at a younger age as compared to the males. Further, we found that meningioma was 2.3 times more common in females as compared to the males. These findings also corroborated with Magill et al who found females were 2.8 times more prone to develop meningioma as compared to the males.[6] Therefore, female gender is a possible risk factor for the development of meningiomas. In addition there is some hormonal influence too that is implicated in the development of meningiomas as females in the reproductive age group are more likely to be affected with meningiomas. But t-test, however, showed that there was no significant difference in mean age of males and females (t48=1.92;p=0.06). We also found that only 2% of the patients were in the age group of <15 years. These findings synced with Mehta et al who found that 1.92% of the cases belonged to the age group of 0-18 years.[7] Thus, further implicating the role of hormonal influence in the development of meningiomas. Early morning headache was the most common symptom (48%) with which the patients presented to us, possibly due to the raised intracranial pressure; intracerebral location (cerebral convexity) accounted for 58% of the tumours. Similar observations were also found by Patil et al who found that headache was the most common symptom in a study conducted on 568 CNS tumours of which 87 were meningiomas; they also proposed that intracranial location (90.8%) was the most common location and cerebral convexity was the most favored site.[8] This study revealed that 48.5% of the female patients had a history of hormone intake (OCP/HRT) but the results were not statistically significant (Z=0.39;p=0.69). However, Jhawar et al, found that the relative risk for meningiomas in pre-menopausal age group consuming Oral contraceptive pill (OCP) was 2.48 as compared to post menopausal women taking hormone replacement therapy(HRT), where the relative risk was 1.86.[9] These observations further point towards the role of hormone receptors in the development and growth of meningiomas. In addition, we also found a positive history of smoking in 40% of our patients. Phillips et al however, found that passive smoking from a spouse (both male/female) were associated with an increased risk of meningioma especially for an increased duration (p=0.02).[10] This study also revealed that 16% of the patients had a family history of meningiomas. Whereas Claus et al who studied 1124 cases of meningioma found that patients of meningioma were more likely to have a first degree family history of meningioma as compared to the controls (OR 4.4, 95% CI 1.6-11.5).[11] We also found that 10 patients out of the 50 patients studied (20%) had a previous history of meningioma. Recurrence in meningioma has also been studied by Guarnaschille et al, who found that among the 333 cases of meningioma 31 cases reported a recurrence accounting for 9.3% of the cases.[12] Recurrence can be attributed to the genetics involved in the development of meningioma and possible association of mutations involving NF2 gene. We found that 43 out of 50 (86%) were WHO grade I meningiomas, histopathologically WHO grade-I meningiomas were significantly higher than other WHO grades (Z=10.75; p<0.0001). Chi-square (χ^2) test showed that there was a significant association between histological grade and PR expression of the patients (=16.85; p=0.0002). Roser et al also found that PR expression was lower in grade II and grade III meningiomas as compared to grade I meningiomas (p <0.0001).[13] Authors also found that there was also a significant association between histological subtype and PR expression of the patients (=50.00;p<0.0001). Of all the subtypes that were positive for PR, Meningothelial meningioma was most common (38%) followed by Transitional meningioma (28%). However, Fibroblastic meningioma (8%), Angiomatous meningioma (6%), Psammomatous (4%) and Microcystic meningioma (2%) were also PR positive. However, Roser et al found that meningothelial and fibromatous subtypes had a statistically significant relation with PR expression (p<0.0001) whereas amongst the other subtypes no such relation was found.[13] Authors further found that amongst the recurrent cases most were PR positive (90.0%) and the results were statistically significant (Z=11.31;p<0.001). However, Roser et al did not find any relation between recurrence and PR status.[13] Furthermore, we also found that there was a significant association between female gender and PR expression of the patients (p=0.0005). Positive PR expression was 22.66 times more for female patients as compared to male patients and this

was statistically significant [OR-22.66 (2.41, 213.11);p=0.0005]. Positive PR expression was 2.48 times more for the patients with age<50 years as compared to the patients with age≥50 years. This attribute could be an explanation to the increasing number of cases of meningioma amongst the females as compared to the males and the role of hormone receptors in the growth of meningiomas. In addition, women in the reproductive age group could also provide a possible explanation to the hormonal influence on the growth of meningiomas. Further, PR positivity in low grade (Grade I) meningiomas also points towards the females being affected with lower grade meningiomas as compared to the males. Furthermore, association of several hormone related tumours especially uterine fibroid, fibroadenoma and endometriosis with meningiomas also indicates a possible hormonal milieu in the pathogenesis of meningiomas. These observations suggest that progesterone plays a significant role in the growth of meningiomas and thus, anti-progestational agents like mifepristone that acts on the progesterone receptors (PR) at much lower concentrations than progestins and inhibits PR could play a role in the medical management of meningiomas.

Hence, epidemiological parameters involoved in meningiomas have provided significant insights to the pathogenesis of meningiomas. The increasing tumour burden of meningiomas especially amongst the female population indicates a close relation between positivity for hormone receptors like PR and increased intake of OCP/HRT by females at large over the past decade. This observation could possibly open newer treatment avenues in the management of meningiomas by drugs targeting hormone receptors especially anti-progestational agents like mifepristone which could possibly control tumour growth by inhibiting the progesterone receptors (PR) found in most meningiomas.

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Ethical approval: Not required

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