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RESEARCH ARTICLE

A POTENTIAL ROLE OF Ki 67, PR and VEGF IN DETERMINING THE TUMOUR BEHAVIOR OF MENINGIOMAS

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ABSTRACT

Background: Meningiomas are traditionally considered as benign tumours with an aggressive potential. Utilization of markers for proliferation and neoangiogenesis in combination with hormone receptor study can aid in the identification of a subset of biologically aggressive and morphologically benign tumours.
Aim: The study aims at determining the potential role of Ki 67, PR and VEGF in assessing the tumour behavior.
Material and Method: This observational study included 50 patients who underwent surgery for meningioma at our hospital during the period of February 2016 to July 2017. Formalin fixed paraffin embedded blocks were prepared and subjected to hematoxylin and eosin staining. Immunohistochemical staining was done for Ki-67, PR, VEGF and CD34 using standard immunoperoxidase techniques.
Results: Ki 67 LI was higher in males as compared to females, in grade II and grade III as compared to grade I, in recurrent cases as compared to nonrecurrent cases and in PR negative cases as compared to PR positive ones. VEGF was also strongly expressed in high grade and recurrent meningiomas. However, few cases of grade I meningiomas revealed a stronger VEGF expression and a higher Ki67 LI as compared to the conventional grade I meningiomas, probably due to the increased likelihood of future recurrence and malignancy in such cases.
Conclusion: Ki 67 and PR bear an inverse correlation with respect to the grading of meningiomas. Further, VEGF also has a potential role in assessing the aggressiveness of meningiomas and in instituting targeted management of meningiomas.

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INTRODUCTION

Meningiomas are the most common primary brain tumors accounting for approximately 15% of all intracranial neoplasms (Shah *et al.,* 2013). It is also the most common intradural spinal tumor. Meningiomas are neoplasms, thought to derive from arachnoidal cap cells in the meningeal covering of the brain and spinal cord. They most commonly occur in the fourth to sixth decade life, with a mean age of 45 years at the time of the diagnosis. Meningiomas are classified into three grades according to World Health Organization (WHO) 2007. The grading has implications on the management. Grade I tumors are treated with surgery alone whereas Grade II and III are treated with surgery and radiotherapy. Grading system based on histopathological features has certain limitations in predicting the exact tumour behavior and future recurrence. Amongst the various techniques available to measure cell proliferation, Ki67 is the most widely used immunohistochemical marker. Ki-67 is a non-histone protein that is expressed in the proliferative phase of the cell cycle (Perry *et al.,* 1998). Further, it is well known that meningiomas frequently express progesterone receptor (PR) but estrogen receptor (ER) expression is rarely seen (Perry *et al.,* 2000). Several studies in the past have shown that there is a decrease in PR expression from low to high grade meningiomas. Hence, cell proliferation indices as measured by Ki-67 in conjunction with hormone receptor study may be used as an objective method for predicting the tumor behavior (Roser *et al.,* 2004). In addition, VEGF is also a potent marker for establishing tumour aggressiveness. VEGF shows increased cytoplasmic expression in Grade II and Grade III meningiomas. Amongst the Grade I meningiomas angiomatous meningiomas show increased VEGF expression. Transitional & meningothelial show a moderate expression of VEGF, whereas fibroblastic

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shows the least of the VEGF expressions. Increased VEGF is associated with a poor prognosis & increased recurrence (2013Dharmalingam *et al.,* 2013). Further, radiologically peritumoural brain edema(PTBE) has also been correlated with increased VEGF expression and a poor outcome (Jack Hou *et al.,* 2013).

Aims and objectives

In the present study, we aim to study the progesterone receptor (PR) status in different histological grades and subtypes of meningioma and correlate it with the expression of Ki-67 proliferation index. We also aim to study the expression of vascular endothelial growth factor (VEGF) in various histological grades and subtypes of meningiomas. In addition we also intent to correlate the expression of VEGF with the peritumoural brain edema (PTBE) seen radiologically.

MATERIALS AND METHODS

This is an observational study. The study included 50 patients who underwent surgical treatment for meningioma at a tertiary care medical institute (NRSMCH, Kolkata) during the period of February 2016 to July 2017. The study was approved by the institute ethics committee. The clinical details were collected from the case records and the radiological findings were recorded from CT/MRI scans.

Histopathology

All tissue samples were collected in 10% neutral buffered formalin and processed for routine histopathological examination. Five micrometers thick sections from formalin fixed paraffin embedded (FFPE) blocks were cut and stained with hematoxylin and eosin for histopathological diagnosis. The histomorphological features that are associated with aggressive behavior are loss of cytoarchitecture, increased cellularity, high mitotic activity, presence of necrosis, nuclear pleomorphism and invasion of brain parenchyma. On the basis of these parameters the tumours were graded according to the WHO grading system (Perry *et al.,* 2007).

Immunohistochemistry (IHC)

For IHC staining, 3 μm thick sections from FFPE blocks were taken on poly L Lysine coated slides and subjected to immunohistochemistry by the labeled standard immunoperoxidase methods with pre-diluted monoclonal antibody of Bio-Genex (USA). The following antibodies were used: monoclonal mouse antihuman PR antibody (Dako, Copenhagen, Denmark), MIB-1(mouse monoclonal antibody against KI-67, Dako), CD34 (mouse monoclonal antibody, Dako), VEGF (rabbit polyclonal antibody against VEGF165 isoform, Biogenex). The antigen retrieval was achieved by the heat-induced epitope retrieval method in anhydrous citrate buffer pH 6.0 after TRIS buffer wash. The endogenous avidin-binding activity was blocked by adding 1 drop of Hi Def Peroxidase Block and waiting for 10 minutes. The sections were incubated in primary antibody for 60 minutes. Hi Def Polymer horse radish peroxidase (HRP) label was used as secondary antibody and 3, 3'-diaminobenzidine (DAB) as the chromogenic substrate. Appropriate positive and negative controls were run. The proliferation index was calculated using the MIB-1 antibody. The Ki-67 LI was determined by recording the percentage of positively staining tumor cell nuclei out of 1000 tumor cell nuclei. The hot spots (regions with the most immunostaining) were used in the determination of the labeling index and the immunostaining results were evaluated at high magnification (400x). Reactive lymph node was used as a positive control and the mean of Ki-67 LI was derived. For PR, section from breast tissue was used as a positive control (Karabali and Sav, 2006). The PR status was determined by a semiquantitative scoring scale with respect to staining intensity (intensity score) (graded as: 0- absent; 1- weak; 2- moderate; and 3- strong) and percentage of positive tumor cells (proportional score) (0- indicating the absence of positive nuclei; 1- the presence of <10% positive tumor nuclei; 2- an estimated 10–50% positive nuclei; 3- 51–80% positive tumor nuclei; and 4- >80% positive tumor nuclei). Total immunoreactive score (TIRS) was calculated for each case by multiplying the intensity score (IS) by the proportional score (PS), producing a TIRS which range from 0 to 12. Tumors with a TIRS of 2 or more were considered as PR positive (Karabali and Sav, 2006). TIRS= IS X PS ---------» (0-12) ----------» ≥2 positive (Roser *et al.,* 2004).

VEGF expression was assessed by using a scoring system proposed by Raica *et al*. 2007. Both intensity and percentage positivity were analyzed. SCORE 0 – negative; SCORE 1 - weak reaction in less than 10% of tumor cells; SCORE 2 - weak to moderate reaction in 10-50% of tumor cells ; SCORE 3 - strong intensity in more than 50% of tumor cells Angiogenic potential of meningioma was evaluated by measuring intratumoral Microvessel density (MVD). The MVD (calculated only in few cases with high VEGF expression) was counted by assessing immunohistochemical expression of CD34 which binds to endothelial cells. MVD was assessed in three "most vascular areas" (hot spots) as described by (Weidner 1991 & 1999). The area containing the maximum number of discrete microvessels were identified by using scanner objective (40x). Individual microvessels were counted using high power objective (400x). MVD is defined as the number of manually counted vessel per high power field taken as the average from three hot spot counts.

RESULTS

A total of 50 cases were studied. Age ranged from 8 years to 77 years (Median: 45.50 years). 76% patients were in the age group of 31-60 years ($p<0.0001$). There were 35 female patients and 15 male patients. Proportion of females (70.0%) was significantly higher than that of males (30.0%) ($p<0.001$). Headache (44.0%) was the most common symptom followed by seizures (28.0%). According to site parasagittal region (56%) was most commonly involved followed by spinal and sphenoid. Only 11(28.6%) had a history of other hormone related tumours, out of which fibroid was most common (20.0%) and this was significantly higher ($Z=3.02;p=0.0025$). Most of the cases were histopathologically Grade-I (86.0%) and this was statistically significant ($Z=10.75$; $p<0.0001$) (Table 1). Ki 67 labeling index in most of the cases ranged between 4-20 (54.0%) followed by a labeling index of <4 (44.0%). Only 2.0% had a labeling index of >20 (Table 2). Most of the cases were PR positive (86.0%) and this was significantly higher than PR negative cases ($Z=10.18;p<0.001$) (Fig. 1). 58.0% cases had VEGF score of 2 which was significantly higher ($Z=4.58;p<0.001$). 16% had a score of 1 whereas 26% had a score of 3 (Fig 3). MVD (CD34 staining) was done for 13 patients who showed a high VEGF expression.

Table 1. Distribution of histological grade

Histological grade	Number	%
Grade-I	43	86.0%
Grade-II	5	10.0%
Grade-III	2	4.0%
Total	50	100.0%

Table 2. Distribution of Ki 67 LI

KI 67 labeling index (%)	Number	%
>20	1	2.0%
4 -20	27	54.0%
<4	22	44.0%
Total	50	100.0%

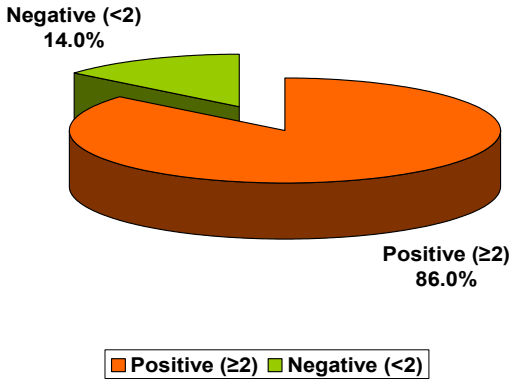

Fig. 1. Pie Chart showing PR expression in meningioma

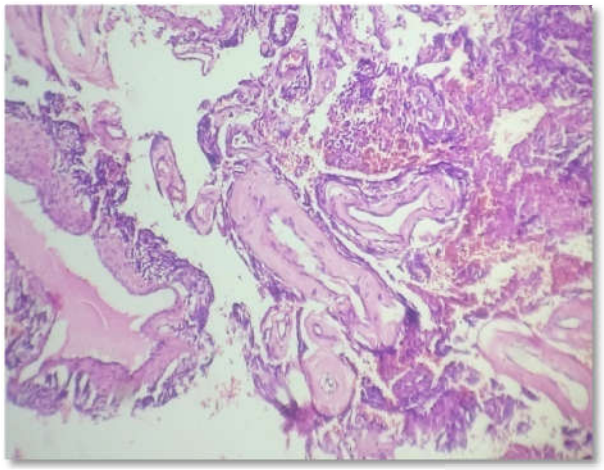

Fig. 2. Angiomatous meningioma (H&E, 100X)

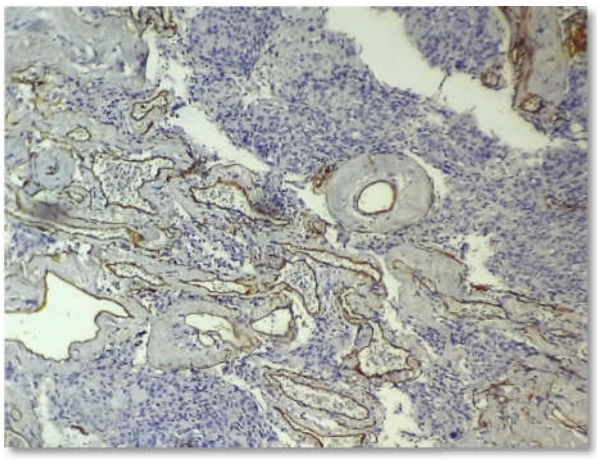

Fig. 2A. CD 34 staining highlighting the blood vessels in angiomatous meningioma(CD34, 100X)

Table 3. Distribution of Histological Grade and VEGF Expression

Histological Grade	VEGF expression			TOTAL
	Score 1	Score 2	Score 3	
Grade I	8	29	6	43
Row %	18.6	67.4	14.0	100.0
Col %	100.0	100.0	46.2	86.0
Grade II	0	0	5	5
Row %	0.0	0.0	100.0	100.0
Col %	0.0	0.0	38.5	10.0
Grade III	0	0	2	2
Row %	0.0	0.0	100.0	100.0
Col %	0.0	0.0	15.4	4.0
TOTAL	8	29	13	50
Row %	16.0	58.0	26.0	100.0
Col %	100.0	100.0	100.0	100.0

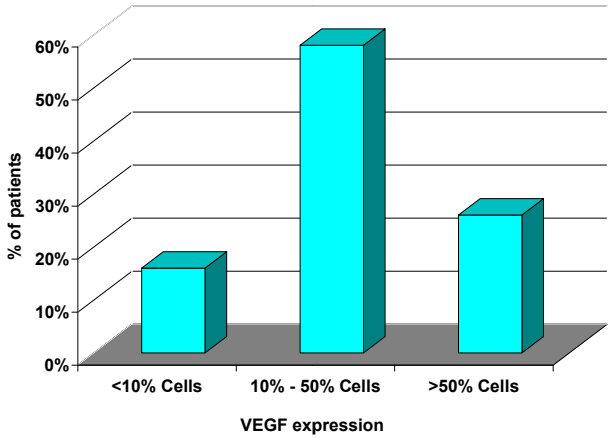

Fig. 3. Bar Graph showing VEGF expression in meningiomas

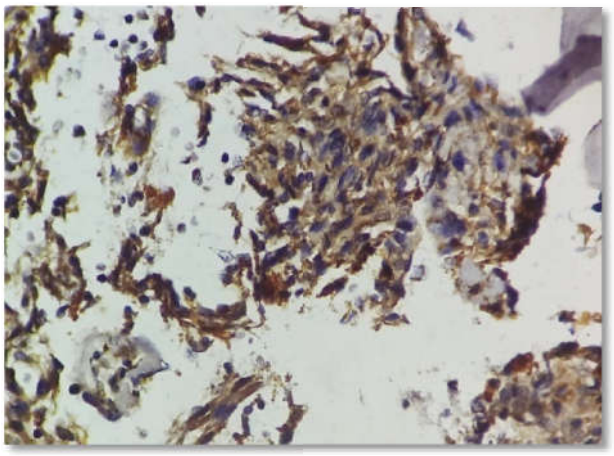

Fig 3A. VEGF expression in atypical meningioma(VEGF, 400X)

This was done to see the correlation between the angiogenic potential of meningioma and VEGF expression (Fig 2, 2A). The mean (±s.d.) of MVD (CD34 staining) of the patients was 5.35±1.39 with range 4.0 – 8.0 and the median was 6.0. The risk of positive PR expression was 22.66 times more for female patients as compared to male patients and the risk was significant [OR-22.66 (2.41, 213.11);p=0.0005]. Test of proportion has showed that a larger proportion of cases with Ki 67 LI <4 belonged to WHO Grade-I and this was statistically significant (Z=12.06;p<0.0001) whereas Ki 67 of 4-20 and >20 were mainly of WHO Grade II and Grade III (Fig 5,5A). Chi-square (χ^2) test showed that there was significant association between Histological Grade and PR expression of the patients (p=0.0002). PR was negative for high grade (grade II and grade III) meningiomas (Fig 4, 4A).

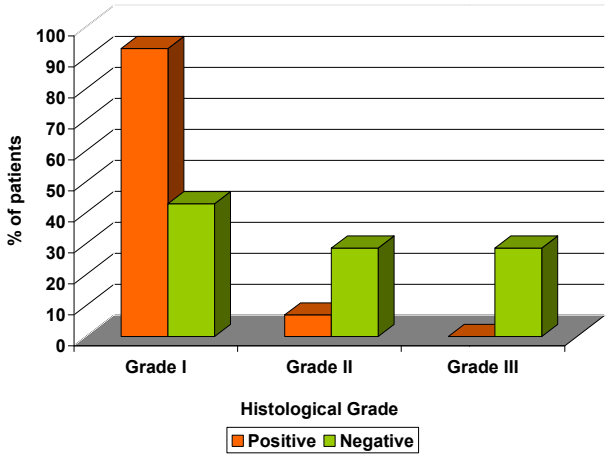

Fig. 4. Bar Graph showing histological grade and PR expression

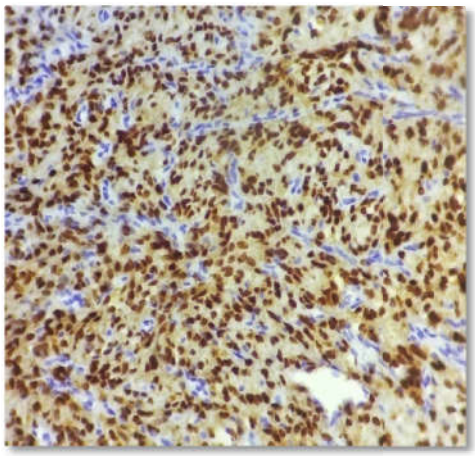

Fig. 4A. PR expression in meningothelial meningioma (PR, 100 X)

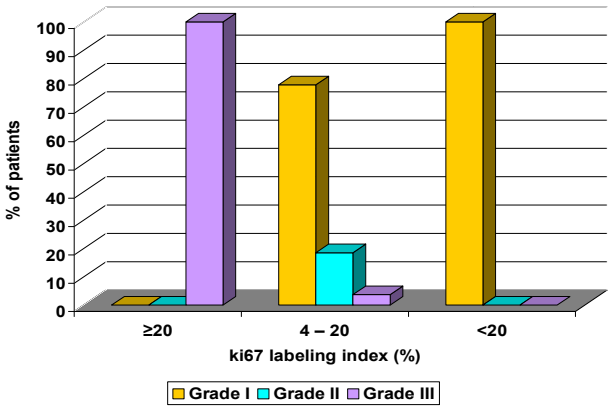

Fig. 5. Bar Graph showing histological grade and ki67 expression

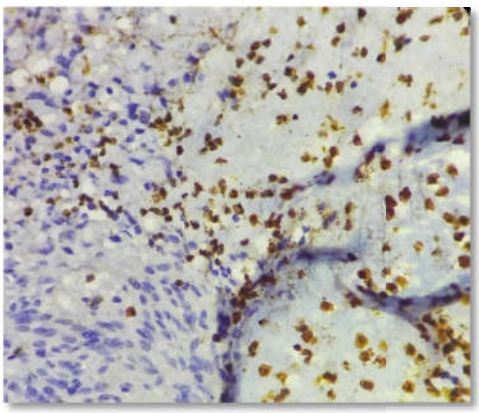

Fig 5A- Ki 67 LI in atypical meningioma (Ki 67, 100X)

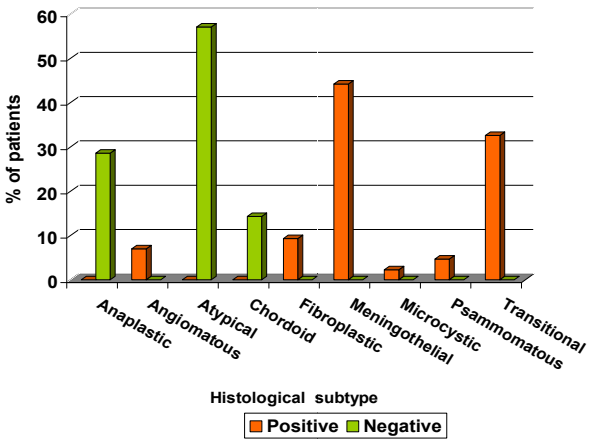

Fig. 6. Bar Graph showing histological subtype and PR

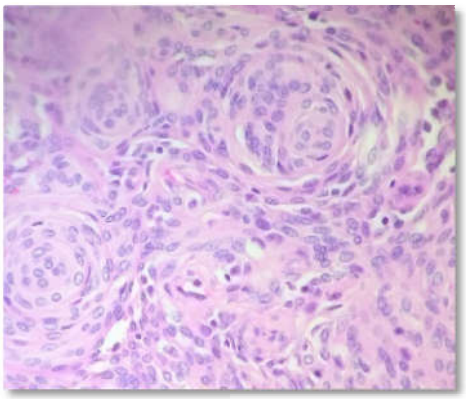

Fig. 6A. Whorls in meningothelial meningioma (H&E, 400X)

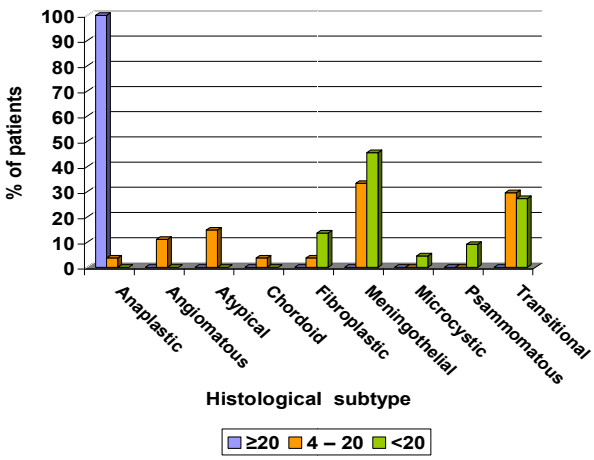

Fig. 7. Bar Graph showing histological subtype and Ki 67 LI

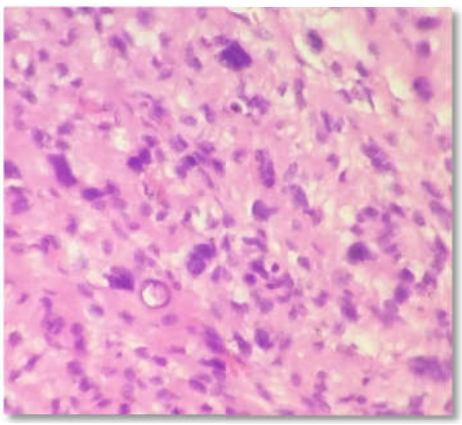

Fig. 7A. Anaplastic meningioma (H&E, 400X)

Corrected Chi-square (χ^2) test also showed that there was significant association between histological subtype and PR expression of the patients ($p<0.0001$). Atypical, chordoid and anaplastic meningiomas were PR negative (Fig 6, 6A). Corrected Chi-square (χ^2) test further revealed that there was a significant association between histological subtype and Ki67 labeling index (%) of the patients ($p<0.0001$). Ki 67 LI was >20 and in the range 4-20 for anaplastic, atypical and chordoid meningiomas, however, some of the histologically benign but immunohistochemically aggressive WHO grade I meningiomas (44% of grade I meningiomas) had a Ki 67 LI in the range of 4-20, although maximum WHO grade I meningiomas had a Ki 67 LI of <4 (Fig 7, 7A). The mean (±s.d.) Ki 67 labeling index of 10 recurrent cases of meningioma was 11.43±4.22% with range 7.2 – 19.8% and the median was 10.45%.The Ki 67 labeling index of all the recurring cases was between 4 – 20 (100.0%). Further, as per Pearson's Correlation Co-efficient a significant negative correlation was found between ki67 labeling index (%) and PR expression ($r = -0.8834$; $p<0.0001$). Thus the value of PR expression decreased with the increasing value of Ki67 labeling index (%) (Fig 8).

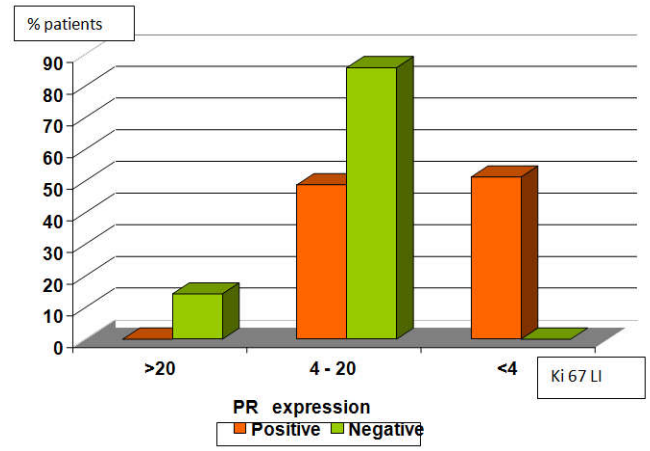

Fig. 8. Bar Graph showing correlation between Ki 67 and PR

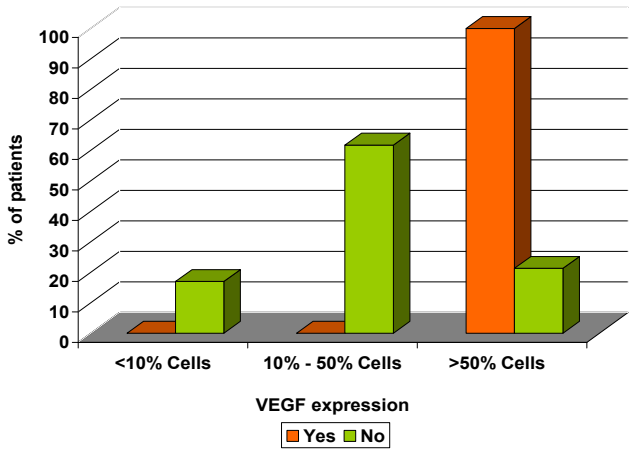

Fig. 9. Bar Graph showing VEGF expression and PTBE

Corrected Chi-square (χ^2) test showed that there was significant association between histological grade and VEGF expression of the patients ($p<0.0001$). All cases of WHO grade II and grade III meningiomas had a high VEGF expression with a score of 3. However, 6 cases of WHO grade I meningiomas also had a high VEGF expression with a score of 3. This category probably represents the histologically benign but immunohistochemically aggressive meningiomas (Table 3). Corrected Chi-square (χ^2) test showed that there was significant association between histological subtype and VEGF expression of the patients ($p<0.0001$). Atypical and anaplastic meningiomas show a very high VEGF expression with a score of 3. Whereas amongst WHO grade I meningiomas angiomatous subtype shows maximal VEGF expression (score 3), followed by meningothelial. Amongst the radiological parameter considered VEGF expression was significantly high ie, score 3 in patients with PTBE, ascertained radiologically (Fig 9, 10).

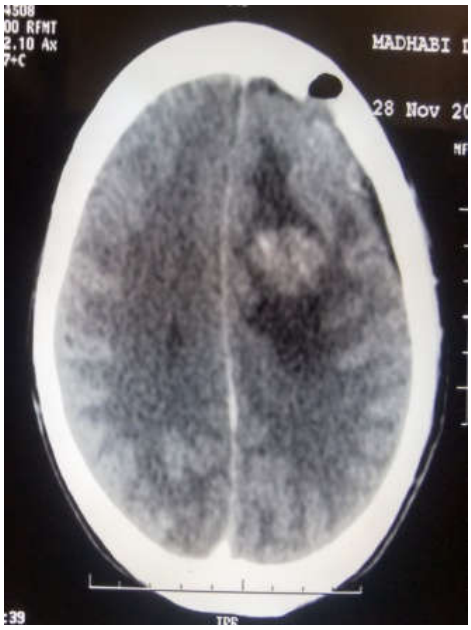

Fig 10. CT Brain showing a heterodense mass in left parietal area with perilesional brain edema (PTBE)

DISCUSSION

Factors implicated in assessing the prognosis of meningiomas include clinical and histopathology related factors. Amongst the clinical factors, younger age and male sex are associated with a worse prognosis (Perry *et al.,* 2007). Besides clinical, histopathological factors like grade and subtype also play a significant role in assessing the prognosis. And besides histomorphology immunohistochemistry (IHC) also aids in establishing the aggressiveness of meningiomas. Amongst the several IHC markers Ki67, PR and VEGF play a significant role in assessing tumour prognosis. In the present study we use the above markers to establish the correlation these markers bear with the several histological grades and subtype of meningiomas. The study was conducted on 50 subjects diagnosed of primary or recurrent meningioma histopathologically. The mean age (mean ± s.d.) of the patients was 46.84±13.54 years with range 8 - 77 years and the median age was 45.50 years. Test of proportion showed that the proportion of the patients in the age group 31-60 years (76.0%) were significantly higher than other age group ($Z= 8.51$; $p<0.0001$). Only 2.0% of the patients were in the age group <15 years. Similar results were also found by Nuaimy *et al.,* 2012 and Mukherjee *et al.,* 2011. The ratio of male and female (Male**:** Female) was 1.0**:**2.3. Proportion of females (70.0%) was significantly higher than that of males (30.0%) ($Z= 5.65$; $p<0.001$). Similar findings were also found by Shayanfar *et al.,* 2010 Headache (44.0%) was the most common symptom

followed by seizures (28.0%) and this was significantly higher (Z=2.35; p<0.05). Similar results were also obtained by Shah *et al.,* 2013 however, Dharmalingam *et al.,* 2013 found visual loss due to raised intracranial tension as the most common symptom (43.5%) followed by seizures. Amongst the 50 cases 10 cases (20.0%) had previous history of meningioma whereas out of 68 cases studied by Rao *et al.,* 2013 6 cases were recurrent. Only 11(28.6%) had any other associated hormone related tumours out of which fibroid was most common (20.0%) and it was significantly higher (Z=3.02;p=0.0025), similar findings were found by Claus *et al.,* 2013 Intracranial location was most common, amongst which parasagittal was the site of predilection (56%). These results were concordant but lower than those found by Mukherjee *et al.,* 2011 (intracranial meningiomas: 85%). Radiologically Peritumoural brain edema (PTBE) was found in 6.0% of the patients. These results were comparatively very low as compared to the study conducted by Reszec et al who found 92 out of 136 (67%) cases to have PTBE (Reszec *et al.,* 2015). Most of the cases were histopathologically WHO Grade-I (86.0% of the patients) and this was significantly higher (Z=10.75;p<0.0001). Similar findings were also reported by Shayanfar *et al.,* 2010 and Mukherjee *et al.,* 2011.

The mean (±s.d.) Ki 67 labeling index of the patients was 7.09±5.74% with range 1.3 – 20.5% and the median was 4.15%. As per Ki 67 LI most of the cases had a Ki 67 labelling index in the range of 4-20(54.0%) followed by a labeling index of <4 (44.0%) (Z=1.41; p=). Only 2.0% had a labeling index of >20. Similar findings were observed by Nuaimy *et al.,* 2012. However, Mukherjee *et al.,* 2011 and Nagashima *et al.,* 2013 found a Ki 67 labelling index of 0.6-15% and 0.4-16.4% respectively. The mean (±s.d.) of PR expression of the patients was 7.56±4.43% with range 0.0 – 12.0% and the median was 8.0%. Most of the cases were PR positive (86.0%) and this was significantly higher than that of negative PR expression (Z=10.18; p<0.001). Similar findings were also found by Nuaimy *et al.,* 2012 and Nagashima *et al.,* 1995 (72% cases were PR positive) whereas Mukherjee *et al.,* 2011 found 65% cases to be PR positive. Corrected Chi-square (χ^2) test showed that there was significant association between gender and PR expression of the patients (p=0.0005). The risk of positive PR expression was 22.66 times more for female patients as compared to male patients and the risk was significant [OR-22.66 (2.41, 213.11); p=0.0005]. Similar associations were also found by Shayanfar *et al.,* 2010 who found that 86.8% females were PR positive while we found a higher percentage (97.1%) of females to be PR positive. Out of the male population Shayanfar *et al.,* 2010 found 68% cases to be PR positive as compared to ours where the positivity was only 60%. The mean (±s.d.) VEGF expression of the patients was 2.10±0.64 with range 1.0 – 3.0 and the median was 2.0. Most of the cases showed a VEGF score of 2 (58.0%) which was significantly higher (Z=4.58; p<0.001). This was however, contrary to the results found by Dharmalingam *et al.,* 2013 who showed that 34.78% cases had a VEGF score of 1 whereas only 28.3% cases revealed a score of 2. Microvessel density (MVD) as determined by CD34 staining, was done for 13 patients who showed a high VEGF expression. This was done to see the correlation between the angiogenic potential of meningioma and VEGF expression. The mean (±s.d.) MVD (CD34 staining) of the patients was 5.35±1.39 with range 4.0 – 8.0 and the median was 6.0. PTBE on radiology was present for 3 cases (6%) and these cases showed a very high VEGF expression (score 3- strong and >50% Cells positive). However, Nassehi (2013) observed PTBE in 43 out of 101 meningiomas, and also correlated the presence of PTBE with increased VEGF expression. Hou *et al.,* 2013 also found a strong relationship between VEGF expression and PTBE in meningiomas. Markovic *et al.,* 2013 showed that PTBE has a significant influence on the prognosis of meningioma in terms of increased risk of morbidity and postoperative complications. Test of proportion showed that PR was positive (93%) in all patients of Grade-I meningiomas and this was significant (Z=11.12; p<0.0001). The result was however lower (70% positivity) by Mukherjee *et al.,* 2011 Test of proportion also showed that a larger proportion of cases with Ki 67 LI <4 belonged to WHO Grade-I and this was statistically significant (Z=12.06; p<0.0001). Similar findings were also found by Nuaimy *et al.,* 2012 and Mukherjee *et al.,* 2011 in grade I meningioma (ki 67 LI 1.8±3.5).

Corrected Chi-square (χ^2) test showed that there was significant association between histological subtype and PR expression of the patients (p<0.0001). Atypical and anaplastic meningiomas were PR negative. The results were consistent with Nagashima *et al.,* 1995. This could also be attributed to the gender difference in meningiomas, showing a male preponderance in having atypical and anaplastic meningiomas. Test of proportion showed that proportions of cases with ki 67 LI>20 and in the range of 4-20 were significantly higher in males as compared to females (p<0.01). Corrected Chi-square (χ^2) test showed that there was significant association between histological subtype and ki67 labeling index of the patients (p<0.0001). Ki 67 LI was >20 and in the range 4-20 for WHO grade III and grade II meningiomas, however, some of the histologically benign but immunohistochemically aggressive WHO grade I meningiomas (44% of grade I meningiomas) had a ki 67 LI in the range of 4-20, although maximum WHO grade I meningiomas had a ki 67 LI of <4. These results corroborated with Nuaimy *et al.,* 2012, Karabali *et al.,* 2006 and Rao *et al.,* who showed that higher values of Ki-67 LI in the low grade meningioma may be due to the possibility of future recurrence or it may be due to focal areas of histologically atypia that may not have been sampled. These findings suggest that biological behavior of meningioma and risk of recurrence cannot be predicted by using conventional histological criteria alone.

This may suggest that Ki-67 may be of importance in identifying a subset of biologically aggressive histologically Grade I meningiomas. Corrected Chi-square (χ^2) test has also showed that there was significant association between histological grade and VEGF expression of the patients (p<0.0001). All cases of WHO grade II and grade III meningiomas had a high VEGF expression with a score of 3. However, 6 cases of WHO grade I meningiomas also had a high VEGF expression with a score of 3. This category probably represents the histologically benign but immunohistochemically aggressive meningiomas. These findings corroborated with the findings of Dharmalingam et al[5] who showed that 100% of grade II and grade III meningiomas were strongly positive for VEGF whereas only 65% of grade I meningiomas showed a VEGF positivity. Corrected Chi-square (χ^2) test showed that there was significant association between histological subtype and VEGF expression of the patients (p<0.0001). Atypical and anaplastic meningiomas showed a very high VEGF expression with a score of 3. Whereas amongst WHO grade I meningiomas, angiomatous subtype

showed a maximal VEGF expression (score 3), followed by meningothelial. These findings were consistent with those of Dharmalingam *et al.,* 2013.

Conclusion

There is a plausible role of Ki 67, PR and VEGF in assessing the aggressiveness of meningiomas. In addition, PTBE ascertained radiologically also bears an association with increased VEGF expression in meningiomas. Thus, promising newer anti- VEGF targeted treatment in high grade meningiomas can improve patient survival.

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