Clinicopathological study of Meningiomas in a tertiary care center

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ABSTRACT
Meningiomas are a group of common, predominantly benign and slow growing tumours of the meninges. The revised 4th edition of WHO classification of Central Nervous system tumours (2016) has classified them into Grades I, II and III based on their biological behaviour as well as proliferative potential. Recurrence and brain invasion are commonly considered to be found in higher grades. Recent studies have shown that high grade tumours have also been associated with clinical findings such as peri-tumoural brain edema. The purpose of the grading system is to aid in formulating an appropriate management plan. The aim of our study was to analyse the clinical and histomorphological features of meningiomas and evaluate the impact of the current grading system in tumour prognosis. A total of 60 cases were included in our study. They were seen predominantly in females and in the 5th and 6th decades of life, with a propensity to occur in the convexities. The commonest variant was meningothelial meningioma and the commonest grade was Grade I. However, we also noted an increase in Grade II meningiomas due to the definition of brain invasion as an atypical feature in the latest classification. Malignant phenotype such as recurrence was seen in all 3 grades. Hence, we conclude that constant revision of the grading system is necessary to maintain diagnostic accuracy and improve current treatment modalities.

INTRODUCTION
Meningiomas are a group of predominantly benign, slow growing neoplasms of the meninges that arise from the arachnoidal cap cells. They have overtaken glial tumours as the most common central nervous system neoplasms in adults, accounting for approximately 34% of all intra-cranial tumours (Backer-Grondahl et al., 2012). However, they remain uncommon in the paediatric age group, where it accounts for less than 3% of brain tumours (Claus et al., 2005). They commonly occur in the fifth and sixth decades of life, with a female predilection of 2:1. This has been attributed to the possible effect of hormones such as progesterone (Roser et al., 2005; Wolfsberger et al., 2004). Majority of tumours occur within the cranial vault and less commonly in the intraspinal, orbital and epidural areas (Hong et al., 2018). Within the cranium, common sites include the convexities, parasagittal area and sphenoid wing. Few rare cases of extra-neural occurrence, such as lung, have also been reported (Kai Xu et al., 2018). Metastasis is not a conspicuous feature of these tumours.

The biological nature of meningiomas is a complex entity with numerous histological variants. There are a total of 15 subtypes according to the WHO, each with a unique histological picture. They can be completely benign or show atypical features associated with brain invasion or can also be frankly...
malignant with high rates of recurrence, metastasis and mortality. Accordingly, the revised 4th edition of WHO classification of CNS tumour has classified these variants into Grades I, II and III, respectively, based on their propensity to progress or recur. The purpose of such grading was to aid in selecting the appropriate treatment plan and to anticipate poor prognosis. Grade I tumours are considered to be indolent and are treated with surgery alone while Grade II and III neoplasms are treated with surgery and adjuvant radiotherapy and chemotherapy, based on the tumour size, atypia and brain invasion.

In 2016, a revision to the fourth edition of the WHO classification of tumours of the CNS was published, which served as both a conceptual and practical advance over its 2007 predecessor. For the first time, the WHO used molecular parameters in addition to histology to define many tumours of the CNS. Grading criteria in the 2016 classification is derived in part from the reports published in two Mayo Clinic series, which have been since been validated. Brain invasion was introduced as a criterion for the diagnosis of atypical meningioma, WHO grade II. While prior classifications had considered invasion a staging feature rather than a grading feature, it joined a mitotic count of 4 or more as a histological criterion that can alone suffice for diagnosing an atypical meningioma in 2016. As in the past, atypical meningioma can also be diagnosed on the basis of the additional criteria of 3 of the other 5 histological features: spontaneous necrosis, sheeting, prominent nucleoli, high cellularity and small cell change.

Recurrence following an apparently total resection (based on Simpsons grading of surgical resection of meningiomas) is one of the most prevalent problems in the management of Meningiomas. Previous data suggests recurrence rates of histologically benign meningiomas to be in the range of 7-25% while atypical and anaplastic types have a rate of 29-52% and 50-94%, respectively (Perry, 2007). High grade tumours are also associated with a shorter disease-free survival period depending on the extent of resection (Modha and Gutin, 2005).

Therefore, peri-operative identification and stratification of high-risk groups in terms of biological behaviour of meningiomas using the WHO grading system has proved to be useful in proper management. The purpose of our study was to analyse the diverse clinical and histomorphological features of meningiomas and evaluate the impact of the current grading system in predicting the course of the tumour.

The study was conducted in Saveetha Medical College, a tertiary care institute in Chennai, India after obtaining necessary approval from the Institutional Research Board. It was a descriptive and observational retrospective study wherein complete enumeration sampling technique was used. All cases of meningioma received and reported in the Department of Pathology during a period of five years from 2014 to 2019 were collected. In case of recurrent tumours in the same patient who were matched with the UHID, the initial age and diagnosis were taken into consideration and subsequent tumours were not included in our study, thereby eliminating 11 cases. There were a total of 60 cases of meningioma that were included in our study.

Necessary details, such as age, gender and site of the tumour along with presenting complaints, were noted from the case records of the patient maintained in the medical records section, after obtaining prior permission. The appropriate H&E stained slides were retrieved from the Histopathology archives and the slides were reviewed with double blinding technique. The histological features were noted and the tumours were diagnosed and classified into one of the many subtypes. These tumours were also re-graded according to the recent 2016 WHO classification of tumours of the central nervous system. Mitotic activity was assessed in the “hot-spots” by taking the numerical mean of ten non overlapping high power fields or a minimum of 1000 cells, whichever comes first.

Data was entered in MS excel sheet and statistical analysis for correlation between the clinicopathological profile of the tumour and recurrence was done using SPSS 2.0 software system. A p value of < 0.05 was taken to indicate a significant relationship.

RESULTS AND DISCUSSION

During the study period, we received a total of 186 cases of CNS tumours, out of which 71 cases were of meningioma and accounts for 38.17% of tumours. Out of the 60 cases included in our study, there were 41 females and 19 males accounting for 68.33% and 31.67% respectively, with a male to female ratio of 1: 2: 2.

Age of the patients ranged from 15 - 81 years at the time of diagnosis, with an average of 48 years. Majority of the cases were seen in the age group 41-50, which consists of 23 cases (38.33%), followed by 51-60 years, which comprises of 16 cases (26.67%). The least number of cases were seen in the paediatric age group with just one case (1.67%) (Table 1).
### Table 1: Demographic analysis of meningiomas with age and gender

| Age Interval   | Male | Female | Total (n=60) | Total Percentage |
|----------------|------|--------|--------------|------------------|
| 0-20 years     | 1    | 0      | 1            | 1.67%            |
| 21-30 years    | 1    | 2      | 3            | 5.00%            |
| 31-40 years    | 3    | 6      | 9            | 15.00%           |
| 41-50 years    | 5    | 18     | 23           | 38.33%           |
| 51-60 years    | 5    | 11     | 16           | 26.67%           |
| 61-70 years    | 2    | 3      | 5            | 8.33%            |
| >71 years      | 2    | 1      | 3            | 5.00%            |
| **Total**      | **19** | **41** | **60**      | **100%**         |

### Table 2: Descriptive analysis of tumour site

| Site                                      | Total (n=60) | Percentage |
|-------------------------------------------|--------------|------------|
| Convexities                               | 16           | 26.67%     |
| Parasagittal                              | 13           | 21.67%     |
| Cerebello-pontine angle                   | 3            | 5.00%      |
| Base of skull – sphenoid wing             | 6            | 10.00%     |
| Olfactory groove                          | 4            | 6.67%      |
| Intra-Ventricular                         | 2            | 3.33%      |
| Tentorial                                 | 5            | 8.33%      |
| Parafalcine                               | 3            | 5.00%      |
| Suprasellar                               | 1            | 1.67%      |
| Foramen Magnum                            | 1            | 1.67%      |
| Jugular foramen                           | 1            | 1.67%      |
| Spinal                                    | 5            | 8.33%      |

### Table 3: Descriptive and comparative analysis of tumour subtype with gender

| Subtype                        | Male | Female | Total (n=60) | Percentage |
|--------------------------------|------|--------|--------------|------------|
| Meningothelial                 | 5    | 14     | 19           | 31.67%     |
| Fibrous                        | 3    | 5      | 8            | 13.33%     |
| Transitional                   | 2    | 9      | 11           | 18.33%     |
| Angiomatous                    | 0    | 1      | 1            | 1.67%      |
| Psammomatous                   | 1    | 2      | 3            | 5.00%      |
| Microcystic                    | 1    | 1      | 2            | 3.33%      |
| Chordoid                       | 0    | 2      | 2            | 3.33%      |
| Atypical                       | 2    | 5      | 7            | 11.67%     |
| Papillary                      | 2    | 1      | 3            | 5.00%      |
| Anaplastic                     | 3    | 1      | 4            | 6.67%      |

### Table 4: Descriptive analysis of WHO grade of the tumour and correlation with gender and recurrence

| WHO Grade | Gender Male | Gender Female | Recurrence Yes | Recurrence No | Total (n=60) | Percent |
|-----------|-------------|---------------|----------------|---------------|--------------|---------|
| Grade I   | 12          | 32            | 2              | 42            | 44           | 73.33%  |
| Grade II  | 2           | 7             | 4              | 5             | 9            | 15.00%  |
| Grade III | 5           | 2             | 5              | 2             | 7            | 11.67%  |
| **Total** | **19**      | **41**        | **11**         | **49**        | **60**       | **100%** |
Table 5: Comparison of number of cases in each grade with previous studies

| WHO Grade | Our study | Study by Shrilakshmi | Study by Nasrin Samadi | Study by Konstantinos Violaris |
|-----------|-----------|----------------------|------------------------|-------------------------------|
| Grade I   | 76.47%    | 90.63%               | 86.1%                  | 89.82%                        |
| Grade II  | 13.72%    | 7.03%                | 8%                     | 5.82%                         |
| Grade III | 9.80%     | 2.34%                | 5.9%                   | 4.36%                         |

Figure 1: Meningioma subtypes, Grade I (H&E, 400X magnification) 1A: Meningothelial; 1B: Fibrous; 1C: Transitional; 1D: Psammomatous; 1E: Microcystic; 1F: Angiomatous

Figure 2: Meningioma subtypes, Grades II and III (H&E, 400X magnification) 2A: Chordoid; 2B: Papillary; 2C: Anaplastic
A total of 10 intracranial sites were noted, apart from intraspinal location. Commonest location of intra-cranial meningiomas was the cerebral convexity with 16 cases (26.67%), followed by parasagittal with 13 cases (21.67%) in both males and females. Extra cranial, intra-spinal meningiomas encompassed 5 cases and were seen only in females (Table 2).

10 out of the 15 variants described in the WHO classification were noted in our study (Table 3). The commonest subtype noted was Meningothelial meningioma having 19 cases (31.67%), followed by transitional meningioma having 11 cases (18.33%) in adults, in both males and females. Angiomatous variant was the least common variant, constituting 1.67% of cases. Any pathological variant with invasion of adjacent glial tissue was diagnosed as atypical meningioma (Figure 3).

The latest WHO classification of tumours of the central nervous system has grouped the various subtypes of meningiomas into 3 grades. Grade I meningiomas were the most common, accounting for around 73.33% of cases followed by Grade II and Grade III tumours with approximately 15% and 11.67% of cases respectively (Table 4).

Out of 60 cases, a total of 11 cases (18.33%) recurred within next 5 years. It included 4 males and 7 females.

2 out of 11 recurrent cases (18.2% of recurrent cases) were seen in Grade I tumours and both cases were histologically diagnosed as meningothelial variants. 4 cases (36.4% of recurrent cases) were noted in Grade II and all were seen in atypical meningiomas showing brain invasion. The remaining 5 recurrent cases (45.4% of recurrent cases) were seen Grade III, 4 in anaplastic and one in papillary variant.

In other words, merely 4.54% of the Grade I tumours showed recurrence, while 44.44% of Grade II tumours and a staggering 71.42% of Grade III tumours showed tumour recurrence.

Meningiomas have emerged as a major CNS tumour with the identification of malignant variants having highly aggressive behaviour and poor prognosis. Much effort has been put in understanding the pathogenesis behind such variation in clinical behaviour of tumours with similar histogenesis, which has paved way for the continuous revision of the WHO classification of these CNS neoplasms.

During the study period, meningiomas encompassed 32.97% of all CNS tumours received in our department. This finding was similar to studies done by (Ruberti, 2007; Intisar and Patty, 2008; Abdel-Aziz et al., 2011). There was a slight female preponderance of 2.2:1, which correlated with other studies done by (Shenoy et al., 2019; Backer-Grondahl et al., 2012). It was observed in all age adult age groups.

Maximum cases (38.33%) were in the 41-50 years age group, followed by 51-60 years, age group. The predominance of meningiomas in the 5th and 6th decades has also been confirmed by (Shah et al., 2005; Lakshmi, 2015). Only one case was noted in childhood, constituting 1.67%, which was comparable to the findings of (Bhagwati et al., 2009), where paediatric meningiomas accounted for about 1.92% of all cases. Our paediatric case was of male gender and a benign variant.

The most frequently noted location was the cerebral convexities, followed by the parasagittal area and the sphenoid wing in the base of the skull. This was in conjuncture with various other studies done by (Wiemels et al., 2010; Abboud et al., 2009). Supratentorial site was noted to be more often involved than infra-tentorial site. We received 2 cases of meningiomas from rare site such as the intra-ventricular region and were clinically suspected to be ependymomas. Spinal meningiomas are less common than intracranial meningiomas comprising 9.8% of all meningiomas in our study, similar to a study by (Gottfried et al., 2003). Intraspinal meningiomas are common in the 50-60 age group and all 5 cases affected only females. This corresponded to a study done by (Lakshmi, 2015), which showed a ratio of 7:1 in favour of females. However in a study done by (Samadi and Ahmadi, 2007) the F: M ratio was a lower 1:3:1.

Out of 15 variants, the Meningothelial variant was the most common histological type, also seen in...
the studies by (Chatterjee et al., 2011; Challa et al., 2011). Subtypes such as Metaplastic, Secretory, Clear cell and Rhabdoid were not diagnosed in our department.

Metaplastic variant is most rare and constitutes 0.3% in a study by Mayo clinic. All subtypes were more common in females, with the exception of only Papillary and Anaplastic variants, which were seen more frequently in males. There was no significant correlation in the type of the tumor to age. Atypical meningioma was the most common subtype in high grade tumors with a total of 7 cases. This can be attributed to the inclusion of brain invasion as a diagnostic feature of atypical meningiomas and was also reported by (Backer-Grondahl et al., 2012), (Figure 3).

For our study, we revised the initial grading of all the cases as some of these cases were diagnosed prior to the latest WHO classification of 2016. Accordingly, we noticed an increase in the Grade II tumor compared to previous data. Still, Grade I tumors were most commonly observed (Table 5).

There are inconsistent reports regarding the influence of age and gender on the grade of meningioma. (Ildan et al., 2007) reported that both variables have no influence on proliferative activity. Male gender was reported as an independent risk factor for high proliferative potential by (Kasuya et al., 2006). We reported no relevant findings in our study regarding the role of age in the grade of the tumor. However, we noted a slight male predominance in higher grades. Nevertheless, due to lack of adequate number of cases in high grade tumors and other associated co-morbid conditions, we were unable to find any conclusive evidence suggesting male gender as a risk factor.

There was no significant relationship between site of the tumor and its grade in our study although studies by (Volaris et al., 2012) suggests that tumors located in the base of skull are more likely to be benign than in other locations.

Recurrence after seemingly total resection is one of the most prevalent problems in the management of Meningiomas. In our study, we had 11 cases of recurrence accounting for 18.33% of cases. It was equally distributed among males and females. Both cases in parafalcine location recurred with 5 years, indicating that tumors in this location tend to recur as suggested by (Dziuk et al., 1998). The recurrence rate was higher compared to other studies by (Lakshmi, 2015) that showed 5.46% recurrence rate. Notably, the number of cases in Grade II and III were also higher in our study. Chi-square tests showed a significant p value of 0.008, indicating a nearly linear correlation between WHO grade of the tumour and recurrence. This corresponded with a study done by (Shenoy et al., 2019) with strikingly similar results.

CONCLUSIONS

The incidence of meningiomas continues to be on the rise due to various hormonal and environmental factors, making them the commonest central nervous system tumour. The revised 4th edition of the WHO classification has proven to be a useful tool in guiding the post-operative management that is aimed at preventing recurrence. However, taking into consideration the frequency of recurrence in grade I tumors, it has become imperative to evaluate the proliferative potential of all meningiomas and not solely rely on the histological findings. There is a need for constant review and revision of the grading system to maintain diagnostic accuracy and improve current treatment modalities.

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