Original Research Article

The role of peritumoural brain edema in ascertaining the high risk meningiomas

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ABSTRACT

Background: Meningiomas are benign tumours which possess a potential to recur. Peritumoural brain edema (PTBE) has been associated with several complications and future recurrence. This study aims to establish the relation of PTBE in different histopathological grades and subtypes of meningiomas and in addition determines the significance of PTBE in ascertaining tumour recurrence.

Methods: Complete surgical resection samples from 50 meningioma patients were obtained from the neurosurgical department and histopathologically processed. CT (computerised tomography) scans were used for ascertaining the tumour site and PTBE. Patients were followed up yearly for 4 years. Recurrent cases were surgically resected and histologically typed.

Results: Meningiomas were more common in the females (70%) than males (30%). PTBE was found in 56% of the cases. 62% were <50 years of age. No significant association was found between gender or age and PTBE. Cerebral convexity was the most common site (56%). 48.8% of grade I meningiomas (p<0.05) and 100% of grade II and grade III meningiomas showed PTBE. Yearly follow up for 4 years showed 10 cases to recur. 90% of these had evidence of PTBE on their pre-operative CT scans. These results were statistically significant (Z=11.31, p<0.001).

Conclusions: Meningiomas are mostly benign entities. However, some histological subtypes possess a potential to recur and invade. It has been found that cases showing radiological evidence of PTBE are at a high risk. Hence, follow up of such cases is essential to improve patient survival.

Keywords: Meningioma, Peritumoural edema, Recurrence

INTRODUCTION

Peritumoural brain edema (PTBE) is one of the most serious complications of meningioma. It not only causes intraoperative complications and difficulty in resection but also causes post-operative seizures and future recurrence. Though meningiomas are classically benign tumours arising from the arachnoidal cap cells, approximately 10% of these tumours show recurrence.¹ Studies have shown that brain invasion in meningiomas is intricately related to PTBE, ascertained via computerized tomography (CT) scans.² Several malignant brain tumours have been associated with PTBE which develops due to the lack of tight junctions in tumour vessels and subsequent leakage of peritumoural edematous fluid. This edematous fluid often contains invasive tumour cells responsible for recurrence.³,⁴,⁵ However, meningiomas being benign tumours with a potential to metastasise are unique to possess such a mechanism for tumour recurrence.
This study aims to establish the relation of PTBE in different histopathological grades and subtypes of meningiomas and in addition determines the significance of PTBE in ascertaining the high risk meningiomas showing tumour recurrence.

METHODS

This is an observational prospective follow up study conducted over a period of 4 years. The study comprised of 50 patients of meningiomas. The patients underwent complete surgical resections of the tumour in the department of Neurosurgery at NRS medical college and hospital, Kolkata. Surgical samples that were obtained were grossed and histopathologically analysed. Tumour grading and subtyping was done according to the new World health organization (WHO) standards 2016. CT scans of the patients were used to determine the site of the tumour and the PTBE associated with the tumour. These patients were followed up yearly for a period of 4 years. CT scans were performed yearly for determining tumour recurrence. Recurrence was defined as meningioma occurring at a site that is same as the previous site or contiguous to the previous resection site. Recurrent tumours were resected and histopathologically typed according to the new WHO standards 2016.

Statistical analysis

Epi Info TM software 3.5.3. was used for the statistical analysis. Statistical analyses were performed to calculate the means and standard deviations (SD). Test of proportion was used to find the standard normal deviate (Z) and Chi-square ($\chi^2$) test was used to find the associations. $p \leq 0.05$ was considered statistically significant.

RESULTS

This study showed that females had a higher propensity (70%) as compared to the males (30%) to develop meningiomas. The ratio of male and female (Male:Female) was 1.0:2.3. These results were found to be statistically significant ($Z= 5.65; p<0.001$). 62% of the cases were <50 years of age whereas the rest (38%) were $\geq$50 years of age. 56% of the cases showed presence of PTBE on their pre-operative CT scans (Table 1).

Table 1: Distribution of PTBE on CT scans.

| PTBE on CT scans | Number | % |
|------------------|--------|---|
| Yes              | 28     | 56.0% |
| No               | 22     | 44.0% |
| Total            | 50     | 100.0% |

However, PTBE did not show any significant association with the gender or age of the patients. CT scans also revealed that cerebral convexity was the most common site (56%) and the results were statistically significant ($Z=6.56; p<0.0001$). Further correlation of PTBE assessed on CT scans (Figure 1) with the microscopic analysis of surgically resected histopathological specimens revealed that 48.8% of WHO grade I meningiomas (p<0.05) and 100% of WHO grade II and grade III meningiomas had PTBE on their pre-operative CT scans. Furthermore, on histomorphological subtyping it was found that besides anaplastic (WHO grade III) and chordoid and atypical (WHO grade II), a few subtypes of WHO grade I meningiomas also revealed PTBE on their respective CT scans. These subtypes included angiomatous, fibrous, transitional and meningothelial meningiomas (Figure 2 and Table 2).

Table 2: Histological subtype and PTBE on CT scans.

| Histological subtype | PTBE on CT scans | Total |
|----------------------|------------------|-------|
|                      | YES | NO |          |
| Anaplastic           | 2   | 0  | 2        |
| Angiomatous          | 3   | 0  | 3        |
| Atypical             | 4   | 0  | 4        |
| Chordoid             | 1   | 0  | 1        |
| Fibrous              | 1   | 3  | 4        |
| Meningothelial       | 9   | 10 | 19       |
| Microcystic          | 0   | 1  | 1        |
| Psammomatous         | 0   | 2  | 2        |
| Transitional         | 8   | 6  | 14       |
| Total                | 28  | 22 | 50       |

These WHO grade I meningiomas represented the histopathologically benign but biologically active high-risk group. Yearly follow up CT scans were done for all 50 cases for a period of 4 years. Of the total, 10 cases recurred. These 10 cases underwent a second surgical intervention. Surgical samples were histo pathologically analysed and it was found that all the cases subtyped as Atypical (WHO grade II) and Anaplastic (WHO grade III) recurred, however, 2 cases of angiomatous meningioma and 1 case each of transitional meningioma and psammomatous meningioma also showed recurrence. Of these 10 recurred cases, 90% had evidence of PTBE on their pre-operative CT scans, however one case of psammomatous meningioma that recurred, did not show any evidence of PTBE on its pre-operative CT scan (Table 3). Hence, PTBE was significantly associated with recurrence of meningiomas ($Z=11.31; p<0.001$).

Table 3: Association of PTBE on radiology with recurrence (n=10).

| PTBE | Recurrent cases | % |
|------|-----------------|---|
| Positive | 9         | 90.0% |
| Negative | 1         | 10.0% |
| Total   | 10        | 100.0% |

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DISCUSSION

Meningioma is classically a benign brain tumour which has a potential to recur even after complete surgical resection in 10-32% of the cases. PTBE as assessed on CT scan has been found to be associated with more than half of the cases. PTBE not only causes intra and post-operative difficulties but also has been implicated as an important factor for causing post-operative recurrence. Though the exact mechanism involved in the development of PTBE is not known, several factors have been previously studied like tumour location and tumour volume, interleukin-6, sex hormone receptors and several others. Recently VEGF (vascular endothelial growth factor) has also been implicated in the development of PTBE. However, none of these factors have convincingly established a role in the development of PTBE.

In the present study we aimed to establish the role of PTBE in ascertaining the high risk meningiomas. In addition, we also established the relation of WHO histopathological grade and subtypes with the PTBE assessed radiologically.

This study thus indicates that meningiomas are tumours which occur with a higher propensity in females as compared to males with a ratio being (male:female) 1.0:2.3. PTBE detected radiologically was found in 56% of our cases. Similar observations were found by Kim et al who studied 86 cases and observed that PTBE was present in 58.1% of the cases. However, Kim et al too could not find any significant association between PTBE and gender. Radiological assessment also revealed that cerebral convexity was the most common site (56%) and the results obtained thereof were statistically significant (p<0.0001). Samadi et al also found cerebral convexity to be the most frequently involved site for meningiomas (31.1%) while studying 238 cases of meningioma over a span of 6 years. Further, it was also analysed that 48.8% of WHO grade I meningiomas showed PTBE on their CT scans (p<0.05) whereas all cases of WHO grade II and grade III meningiomas showed PTBE on their respective CT scans. Furthermore, it was observed that histological subtypes of WHO grade I meningiomas that showed PTBE on their CT scans included angiomatous, fibrous, transitional and meningothelial. In addition, anaplastic, atypical and chordoid meningiomas were also found to illustrate PTBE on their respective CT scans. While a few studies have shown significant findings correlating PTBE with histological grade especially of WHO grade II and grade III and uncommon variants of WHO grade I meningiomas. Moreover, number of studies also showed that of the several types of WHO grade I meningiomas, meningothelial, transitional and secretory variants had a higher tendency to produce PTBE. Further, in this study after a yearly follow up for a period of 4 years it was found that 10 cases recurred. Recurrence was precisely seen in Atypical (WHO grade II) and Anaplastic (WHO grade III) meningiomas. However, a subset of WHO grade I meningiomas with a high-risk potential were also seen to recur. Marciscano et al gave a probable explanation to this recurrence in benign (WHO grade I) meningiomas. He emphasized that such benign (WHO grade I) tumours possessed some atypical areas which predisposed it to recur. He also proved that the chance of recurrence was higher in WHO grade III and

Figure 1: Contrast enhanced CT scan showing a sphenoid wing Meningioma with PTBE.

Figure 2: Meningothelial Meningioma (WHO Grade I), H&E, 400X.
WHO grade II meningiomas being 60-94% and 29-59%, respectively, while the chance of recurrence in WHO grade I meningiomas was found to be 7-25% only. Several studies have tried to provide an explanation as to the increased risk of recurrence in WHO grade II and grade III meningiomas; highercellularity, atypical and brisk mitosis and presence of necrosis possibly are some factors implicated in high recurrence. Further, among other factors that predispose to recurrence, Peritumoural brain edema (PTBE) represents a key factor. Simis et al provided a plausible explanation to the role of PTBE in recurrence of meningioma. He concluded that PTBE was associated with the invasive potential of meningiomas. Further, PTBE is often associated with a higher risk of intraoperative complications like loss of dissection plane at brain-tumour interface; pre and post-operative seizures; postoperative intracranial haematoma and subsequent intracranial hypertension; higher risk of blood transfusion, prolonged hospital stay and post-operative neurological deficit though steroids have been frequently used to counter the PTBE in several brain tumours to lessen the complications during craniotomy, its usage in meningiomas remains inconclusive. PTBE has been found in about 38-67% of meningiomas but its presence has been associated with tumour recurrence. Moussa et al found that tumours showing recurrence were associated with a higher preoperative brain edema index and those with higher brain edema index were associated with lesser time to recur. Further, other factors have also been implicated in tumour recurrence namely, incomplete surgical removal, high grade tumours, variable contrast enhancement seen radiologically, microscopy showing nucleolar prominence and evidence of 2 or more mitosis per 10 high power field.

This study showed that PTBE was significantly associated with several histological subtypes of meningiomas bearing high risk potential. In addition, PTBE was also found in all the cases of WHO grade II and grade III meningioma and a subgroup of WHO grade I meningiomas. This subgroup of WHO grade I meningiomas that showed PTBE on their respective CT scans represents the high-risk group and calls for a follow up in addition to the high grade meningiomas. Follow up of the patients revealed that PTBE was significantly associated with recurrence in meningiomas (Z=11.31; p<0.001), as 90% of our recurrent cases showed preoperative presence of PTBE on their CT scans.

**Limitation**

As the sample size is small, further studies are required to affirm the role of PTBE in ascertaining the high risk meningiomas.

**CONCLUSION**

Peritumoural brain edema is found in approximately half of the cases of meningioma. Its presence not only complicates surgery but also predisposes to future recurrence and increased morbidity and mortality. Therefore, timely follow up of such high-risk patients with PTBE allows to detect tumour recurrence at the earliest and prolongs patient survival. Further, it is reasonable to gear up treatment strategies in meningiomas and target PTBE as an important precursor to the recurrence of meningiomas.

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