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Original Article

Relationship between peritumoral brain edema and Ki-67 antigen labelling index in intracranial meningiomas.

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Abstract:

Introduction: The most common benign non-glial cerebral tumor in adults is a meningioma. In roughly 50–78% of instances, peripheral brain edema (PTBE) is a common observation in meningioma, while it may not be present in others. Although the Ki67 proliferation index may be able to predict the recurrence of tumors in meningioma patients, there is a lack of conclusive evidence and relationships.

Objective:

To enhance evaluation, correlate the Ki67 index of meningioma patients with peritumoral cerebral edema.

Methods:

This cross-sectional study involved 24 patients with meningioma (20 female, 4 male; mean age 39.95 ± 14.54 years). Pre-operative neuroimaging was used to evaluate all patients for the presence of cerebral edema surrounding the lesion using brain MRI and histological confirmation. An immune-histochemical staining known as the Ki-67 index was used to measure proliferative activity. The possibility of a relationship between the levels of the Ki67 index and the existence of PTBE was investigated.

Result:

WHO grade I tumors were identified in approximately twenty-three (95.8%) of the patients with PTBE, mean age 39.95 with 14.54 SD and male to female ratio 5:1. Eight patients (33.3%) were classified as GR1 patients, one as GR2, and the majority of patients (15/62.5%) as GR0 patients. For G1, the greatest level is represented by the mean value of the Ki-67 Index level, which is 7.00. When compared to gender, tumor location, and meningioma type ($p>0.05$), the PTBE grading was statistically significant when it came to the Ki-67 indices ($p<0.05$). Furthermore, the grading of peritumoral edema (PTBE) and the Ki-67 labelling index value exhibited a substantial positive association, as indicated by the spearman correlation test, with a significant p-value <0.05 and a coefficient value of $r = 0.647$.

Conclusion:

Peritumoral brain edema (PTBE)-encircled meningioma had a strong correlation with Ki67 indices.

Keywords: Meningioma, Ki67, Peritumoral Brain Edema, Proliferative Index.

Introduction:

Meningiomas account for about 37% of all central nervous system primary malignancies, are the most prevalent adult benign non-glial intracranial tumors [1]. Their frequency rises with age, reaching a noticeable peak around the fifth decade of life. They are expected to be three times more common in females between the ages of 35 and 54. They mostly affect women, with approximately twice as many instances in females as in males. [2].

Based on their classification of CNS tumors, the World Health Organization (WHO) divided meningiomas into three primary classifications in their 2016 classification: I (benign), II (intermediate), and III (malignant). [3]. While 90% are benign, 6% are atypical, and 2% of meningiomas are malignant, brain imaging utilizing contrast-enhanced CT or MR imaging is the most widely used method for diagnosis, monitoring, and evaluating treatment response. [4].

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However, significant morbidity and mortality from meningioma may result from the tumor's location and size as well as from the existence of peritumoral brain edema (PTBE). while approximately 60% having a perifocal edema [5] Brain herniation from PTBE may eventually occur, increasing intracranial pressure. This could affect the surgical result and is also believed to be a predictor of the difficulty of surgical resection [6]. Meningioma of benign cases may remain clinically silent but when it comes to malignant meningiomas, PTBE is better seen on T2W or FLAIR MRI imaging and corresponds with dimensions, rate of expansion, site, and invasion [7]. Since it is well known that even small meningiomas can result in PTBE that is remarkably prominent, it was wondered if there were any other factors besides tumor site and size that could affect the incidence and severity of PTBE [8] [9].

Since Ki-67 is a highly reliable indicator of the growth fraction of a particular cell population, antibodies directed against the protein are being utilized more frequently as diagnostic tools for various neoplasms [10]. Since PTBE is frequently observed in meningiomas approximately 50~78% cases, Ki-67 immunostaining has been proposed as a means of enhancing the information provided by the grading system and possibly acting as a marker of tumor recurrence in meningioma patients [11]. However, there is insufficient evidence to support a relationship between the Ki67 index and peritumoral edema in meningiomas. For this reason, the purpose of this study was to evaluate whether and how a neurosurgeon may use the Ki-67 labeling index to choose the best follow-up criteria and treatment options.

Methodology

Study Design, participants, and procedure

From March 2019 to September 2020, a cross-sectional sectional face-to-face survey was done with 24 (20 Female and 4 male) patients at Department of Neurosurgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbagh, Dhaka, Bangladesh. Using a purposive sampling technique all patients irrespective of age and sex with intracranial meningioma diagnosed by MRI of brain with contrast who were admitted and underwent surgery for it within the aforementioned period of study and was confirmed by histopathology & immunohistochemistry were included as study population. However, patients having multiple or recurrent meningiomas, history of previous cranial surgery or whole brain irradiation, or steroid intake before preoperative MRI were excluded from the study.

Three readers conducted a retrospective analysis of the MRI results. In cases where there were discrepancies in the readings, the majority of readers' results were considered when making decisions.

In addition, data was collected regarding participants' particulars, clinical features (neurological examination, location of tumor, grading of peritumoral edema) MRI image findings (T2 WI & FLAIR sequence), clinic-radiological findings, histopathology report, and ki-67 value from immunohistochemistry report.

Peritumoral edema

Peritumoral edema is hypointense on T1-weighted images and hyperintense with T2-weighted and FLAIR images. Quantification of peritumoral edema is determined from T2-weighted MRI. Edema was graded as follows: a) GR0 - absent, no evidence of peritumoral hyperintensity on T2- weighted MRI; b) GR1 - focal, hyperintensity 3 cm or less in width on T2-weighted images; c) GR2 - lobar or hemispherical, hyperintensity more than 3 cm in width on T2-weighted images (Figure 1) [12]

Ki-67 labelling index

The expression of Ki-67 is shown in most tumors including glial tumors, and meningiomas. Using a monoclonal antibody, meningiomas' proliferative potential is ascertained by their Ki-67 positivity. Ki-67. Ki-67 labeling index as assessed by section embedded in paraffin using immunohistochemistry (IHC) analysis. Percentage of Ki-67 positive nuclei/1000 tumor cells is termed as labeling index. Meningiomas with high Ki-67 labeling index has a significantly higher tendency of recurrence (Figure 2) [13]

Statistical Analysis

In the current study, the results of the study were performed and the data was processed by utilizing IBM SPSS Statistics program (version 22.0). Results were described in frequencies or percentages. Statistical comparisons were done using Spearman’s correlation test and P value ≤ 0.05 was considered statistically significant.

Ethical Implications

The study got formal authorization from the Bangabandhu Sheikh Mujib Medical University (BSMMU) Institutional Review Board (IRB) (Memo No- BSMMU/2019/13202). Before the study began, every participant or respondent was made aware of it, and their informed written consent was acquired. Participation in this study was completely optional. The privacy of the patient was strictly maintained and didn’t cause any additional harm to the patient.

Results

Demographic Data

The study included 24 cases including 20 (83.3%) of female of intracranial meningiomas which were surgically operated in the hospital.

The mean age of the respondents were 39.95 with 14.54 SD with a male female ratio 5:1. Most of the patients had WHO grade I tumor nearly 23 (95.8%) and regarding the location of the tumor, the most common location were convexity, parasagittal and posterior fossa including 6 (25%) of each. Most of the patients had meningothelial meningioma 18 (75.0%) (Table-1).

PTBE and Ki-67 Index

Most of the patients had G0 15 (62.5%) and G1, G2 had 8 (33.3%) and 1 (4.2%) respectively. The grading of the PTBE was statistically significant with the indices of Ki-67 ($p<0.05$) (Table-2). The mean Ki-67 Index level represents the expansive activity of meningiomas, which was evaluated prospectively for all cases having a highest level 7.00 for G1 (Table-1). Regarding the Ki-67 indices which is statistically not significant with gender, location of the tumor and type of meningiomas ($p>0.05$) (Table-2). There were patients that had Ki-67 indices above 3%. Median Ki-67 value for GR0 is 2.00, for GR1 is 5.00. In GR0, these was range of Ki-67 value from minimum 1.00 to maximum 5.00, in GR1 Ki-67 value from minimum 3.00 to maximum 15.00 (Figure-3). In addition, spearman correlation test was done due the skewed distribution of the Ki-67 labelling index value compared to the grading of peritumoral edema. With a significant p- value of ($P< 0.05$) and a coefficient value of $r = 0.647$, the test demonstrates positive correlation. (Figure-4).

Comparison with other studies

Meningiomas are common primary central nervous system (CNS) tumors that are usually histologically benign, accounting for around 30% of primary adult intracranial tumors [14] [15]. Meningiomas often develop between the ages of 48 and 60, with a mean age of 48 and Alexiou et al. 2010 noted that, the incidence of meningiomas increases with ages, peaks after the fifth decade of life [16]. In our current study, majority of the respondents were among 31-40 years of age (29.1%) of age and second peak among the 21 to 30 years (25.0%) of age with the Mean studies ± SD 39.95 ± 14.54 years of the participants, which concurs with other previous [16]. With a female to male ratio of 2:1 to 2.5:1, meningiomas are diagnosed in women more often than in men; however, other publications have claimed a 3:1 ratio [17]. In our instance, just 20 out of 24 instances were found to be female, indicating a clear gender predominance. Previous findings have demonstrated increased growth rates of meningiomas during pregnancy and the luteal phases of the menstrual cycle, and they suggest that hormonal factors may be responsible for the preponderance of meningiomas in women [18].

Nonetheless, 80% of meningiomas are WHO grade I slow-growing tumors. A benign course is anticipated for WHO grade I meningiomas. Of all meningiomas, 15-20% are atypical meningiomas. One to three percent of instances of meningioma are anaplastic meningiomas, which share clinical traits with other malignant neoplasms [19].

The majority of cases in this study 23 (95.6%) were WHO grade I, which is also the most common in other investigations. Aguiar et al. discovered 28 instances (51%) GR0 group, 19 (34.5%) GR1, and 8 (14.5%) GR2. Simis et al. illustrated that almost 60% of meningiomas are linked to a peritumoral edema. The distribution of cases based on the edema grading in our study appears to be consistent with previous authors' findings, however the overall GR0 percentile is a little bit high, most likely because of the small study group [1]. PTBE is frequently detected in over 50% of meningiomas although, the exact cause of the development of PTBE with meningiomas is unknown, it is thought to be influenced by a number of variables, including patients age, gender, location of tumor and size, histology, and vascularity [20]. Compaction of the cerebral venous system next to the tumor is thought to be the source of increased PTBE, according to an established theory. According to one study, PTBE is brought on by increased permeability through the surrounding white matter fibers of the tumor, while another study proposed that the blood brain barrier is compromised [21]. However, in meningiomas that have been partly resected, higher Ki67 index levels are linked to faster doubling times and higher growth rates [22]. Aguiar et al., reported the mean LIs in the following groups GR0, GR1, and GR2 were 1.49 ± 1.62, 2.78 ± 3.36, and 5.43 ± 3.37, respectively. The mean values of Ki-67 labelling index of this particular study did not correspond to any other authors. This discrepancy is due to the lower number of cases and probably different tissue staining system in the histopathology lab.

Data on the correlation between the Ki67 index and specific variables, such as peritumoral edema, are, however, scarce. In this investigation, our objective was to ascertain whether there was a correlation between the Ki67 index values and the level of peritumoral edema surrounding meningiomas. There are known to be considerable differences in the expression level of Ki67 between benign (G0), atypical (G1), and anaplastic meningiomas (G2) [23]. Perry et al. proposed that a Ki67 index more than 4.2% was suggestive of strong tumor growth activity and recurrence in a study involving 62 cases of meningiomas [24].

In our study, the spearman correlation test was used to compare the grading of peritumoral edema with the Ki-67 labelling index and there was a statistically significant p value ($P<0.05$) and a positive correlation coefficient of 0.647 thus it is possible to suggest a direct association between the two factors. whereas, these two factors were not found to be related in a study by Gawlitza et al. [6]. Meningioma without edema (GR0) in our study had high Ki67 values in some cases, which will direct a neurosurgeon to do a long-term follow-up because there is a high likelihood of recurrence.

In line with our results, Kim B-W et al. proposed in a study of 86 meningioma patients that greater Ki-67 antigen indices are linked to an increased frequency of PTBE. [25]. Although there is a substantial association between PTBE and Ki67 indices in other studies as well [21] [22] [26], more study with a bigger patient group and longer follow-up periods may be important indicator to definitively establish the clinical-relationship due to PTBE's limits and the various factors that influence it.

Strengths, Limitations, and Recommendations

This study is the first one we are aware of in Bangladesh that relates the Ki-67 antigen labeling index to PTBE. To continue with the limitations, the study is limited by its small sample size and its use of sampling from a single specialized facility. Furthermore, the cost and duration of immune- histochemical analysis remain high, and imaging patients using a piece of single-type equipment may help to minimize bias.

According to this study, for improved neurosurgical decision-making about follow-up, intracranial meningioma patients should have a ki-67 antigen labeling index and PTBE should be thoroughly documented during preoperative imaging.

Conclusion:

The current findings of the study confirm that in intracranial meningiomas, there is a substantial positive correlation between peritumoral brain edema and the Ki-67 index. These findings could provide more insight into the significance of proliferation markers and how they can be used to more accurately predict the traits and behavior of meningiomas.

References:

1. Imam N, Elghriany AI, Elshanawany AM, Elhakeem AA. Ki67 Proliferative Index and Peritumoral Brain Edema in Meningiomas: Do They Correlate? A Clinical Study on 56 Patients. Open Journal of Modern Neurosurgery. 2019 Sep 12;9(4):461-71.
2. Shaikh N, Dixit K, Raizer J. Recent advances in managing/understanding meningioma. F1000Res. 2018 Apr 24;7:F1000 Faculty Rev-490. doi: 10.12688/f1000research.13674.1. PMID: 29770198; PMCID: PMC5931261.
3. Harter PN, Braun Y, Plate KH. Classification of meningiomas-advances and controversies. Chin Clin Oncol. 2017 Jul 1;6(Suppl 1):S2.
4. Rockhill J, Mrugala M, Chamberlain MC. Intracranial meningiomas: an overview of diagnosis and treatment. Neurosurgical focus. 2007 Oct 1;23(4):E1.
5. SIMPSON D. The recurrence of intracranial meningiomas after surgical treatment. J Neurol Neurosurg Psychiatry. 1957 Feb;20(1):22-39. doi: 10.1136/jnnp.20.1.22. PMID: 13406590; PMCID: PMC497230.
6. Gawlitza M, Fiedler E, Schob S, Hoffmann KT, Surov A. Peritumoral Brain Edema in Meningiomas Depends on Aquaporin-4 Expression and Not on Tumor Grade, Tumor Volume, Cell Count, or Ki-67 Labeling Index. Mol Imaging Biol. 2017 Apr;19(2):298-304. doi: 10.1007/s11307-016-1000-7. PMID: 27552812.
7. Uduma UF, Emejulu JK, Motah M. Intracranial meningiomas in the present era of modern neuroimaging: diagnostic and management options, with radiological illustrations. Orient Journal of Medicine. 2013 Sep 20;25(3-4):67-74.
8. Tanaka M, Imhof HG, Schucknecht B, Kollias S, Yonekawa Y, Valavanis A. Correlation between the efferent venous drainage of the tumor and peritumoral edema in intracranial meningiomas: super selective angiographic analysis of 25 cases. Journal of neurosurgery. 2006 Mar 1;104(3):382-8.
9. Wang P, Ni RY, Chen MN, Mou KJ, Mao Q, Liu YH. Expression of aquaporin-4 in human supratentorial meningiomas with peritumoral brain edema and correlation of VEGF with edema formation. Genet Mol Res. 2011 Sep 23;10(3):2165-71.
10. Scholzen T, Gerdes J. The Ki-67 protein: from the known and the unknown. J Cell Physiol. 2000 Mar;182(3):311-22. doi: 10.1002/(SICI)1097-4652(200003)182:3<311::AID-JCP1>3.0.CO;2-9. PMID: 10653597.12.
11. Abry E, Thomassen IØ, Salvesen ØO, Torp SH. The significance of Ki-67/MIB-1 labeling index in human meningiomas: a literature study. Pathol Res Pract. 2010 Dec 15;206(12):810-5. doi: 10.1016/j.prp.2010.09.002. Epub 2010 Oct 15. PMID: 20951502.
12. Alvernia JE, Sindou MP. Preoperative neuroimaging findings as a predictor of the surgical plane of cleavage: prospective study of 100 consecutive cases of intracranial meningioma. J Neurosurg. 2004 Mar;100(3):422-30. doi: 10.3171/jns.2004.100.3.0422. PMID: 15035277.
13. Torp SH, Lindboe CF, Granli US, Moen TM, Nordtømme T. Comparative investigation of proliferation markers and their prognostic relevance in human meningiomas. Clinical neuropathology. 2001 Sep 1;20(5):190-5.
14. Challa, S., Babu, S., Uppin, S., Uppin, M., Panigrahi, M., Saradhi, V., Bhattacharjee, S., Sahu,
B. and Purohit, A. (2011) Meningiomas: Correlation of Ki67 with Histological Grade. Neurology India, 59, 204.
15. Bitzer, M., Wöckel, L., Morgalla, M., Keller, C., Friese, S. and Heiss, E. (1997) Peri-tumoural Brain Oedema in Intracranial Meningiomas: Influence of Tumour Size, Location and Histology. Acta Neurochirurgica, 139, 1136-1142. https://doi.org/10.1007/BF01410973.
16. Sanai, N. and McDermott, M.W. (2010) A Modified Far-Lateral Approach for Large or Giant Meningiomas of the Posterior Fossa. Journal of Neurosurgery, 112, 907-912. https://doi.org/10.3171/2009.6.JNS09120.
17. Taghipour, M., Rakei, S.M. and Monabati, A. (2007) The Role of Estrogen and Progesterone Receptors in Grading of the Malignancy of Meningiomas. Iranian Red Crescent Medical Journal, 9, 17-21.
18. Lee, E., Grutsch, J., et al. (2006) Association of Meningioma with Reproductive Factors. International Journal of Cancer, 119, 1152-1157. https://doi.org/10.1002/ijc.21950.
19. Pavelin, S., Becic, K., Forempoher, G., Mrklic, I., Pogorelic, Z., Titlic, M., & Andelinovic, S. (2013). Expression of Ki-67 and p53 in meningiomas. Neoplasma, 60(5), 480-5.

20. Paek, S.H., Kim, C.Y., Kim, Y.Y., Park, I.A., Kim, M.S., Kim, D.G., et al. (2002) Correlation of Clinical and Biological Parameters with Peritumoral Edema in Meningioma. Journal of Neuro-Oncology, 60, 235-245. https://-doi.org/10.1023/A:1021186401522.
21. Tamiya, T., Ono, Y., Matsumoto, K. and Ohmoto, T. (2001) Peritumoral Brain Edema in Intracranial Meningiomas: Effects of Radiological and Histological Factors. Neurosurgery, 49, 1046-1051. https://-doi.org/10.1097/00006123-200111000-00003.
22. Ide, M., Jimbo, M., Yamamoto, M., Umebara, Y., Hagiwara, S. and Kubo, O. (1996) MIB-1 Staining Index and Peritumoral Brain Edema of Meningiomas. Cancer, 78, 133-143. https://-doi.org/10.1002/(SICI)1097-0142(19960701)78:13.0.C O;2-0.
23. Amatya, V.J., Takeshima, Y. and Sugiyama, K. (2001) Immunohistochemical Study of Ki-67 (MIB-1), p53 Protein, p21WAF1, and p27KIP1 Expression in Benign, Atypical, and Anaplastic Meningiomas. Human Pathology, 32, 970-975.
24. Perry, A., Chicoine, M.R., Filiput, E., Miller, J.P. and Cross, D.T. (2001) Clinicopathologic Assessment and Grading of Embolized Meningiomas: A Correlative Study of 62 Patients. Cancer, 92, 701-711. https://-doi.org/10.1002/1097-0142(20010801)92:33.0.CO;2-7.
25. Kim, I.S., Kim, H.D., Kim, K.U., Shin, H.C., Choin, H.J. and Kim, K.H. (1997) Factors Influencing the Development of Peritumoral Brain Edema in Menigiomas. Journal of Korean Neurosurgical Society, 26, 940-945.
26. Bečulić, H., et al. (2019) Correlation of Peritumoral Brain Edema with Morphological Characteristics and Ki67 Proliferative Index in Resected Intracranial Meningiomas. Acta Clinica Croatica, 58, 42-49. https://doi.org/10.