Original Article

Ependymal enhancement on magnetic resonance imaging for the identification of high-grade gliomas

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Abstract

Background: High-grade gliomas have high infiltrative potential and spread along white matter and blood vessels. Enhancement of ependymal lining on magnetic resonance imaging (MRI) is considered as a marker of parenchymal spread of disease. In this study, we aimed to assess the sensitivity, specificity, and positive and negative predictive values of ependymal enhancement (EE) for identification of high-grade glial tumors.

Methods: We reviewed preoperative MRI scans of 94 consecutive patients surgically treated for space occupying lesions of the brain for EE. Assessment for EE was blind to the final histopathological diagnosis of the patient. An enhancement of more than 2 mm was considered positive. Pathologies of these patients were reviewed and matched to the radiological findings. Percentage and proportion of EE in glial and non-glial pathology groups was then calculated and a sensitivity and specificity analysis was performed.

Results: The population included 94 cases (64 males and 30 females) with population mean age 45 ± 15.5 years. Sensitivity of EE in differentiating glioma from total number of cases was 82.61% specificity 35.42% (P value = 0.048). EE had a sensitivity of 67.39% and specificity of 64.58% (P value = 0.002) in identifying high-grade glioma within the glioma group with a positive predictive value of 64.58% (95% CI: 49.46% to 77.83%), negative predictive value of 67.39% (95% CI: 51.98% to 80.46%).

Conclusion: EE has moderate sensitivity and specificity for high-grade gliomas. However, larger sample studies are required for further validation of this observations.

Key Words: Ependymal enhancement, high-grade glioma, tumor spread

INTRODUCTION

Gliomas are the most common primary neoplasms of the brain. These include astrocytomas, oligodendroglioma, and oligoastrocytomas, based on the originating cell. Astrocytomas and oligodendrogliomas are further subdivided based on the histological grade. High-grade gliomas include anaplastic astrocytoma (Grade III

astrocytoma), anaplastic oligodendroglioma (Grade III aoligodendroglioma), and glioblastoma multiforme (GBM, Grade IV astrocytoma).[18] The therapeutic strategies for each of these, tumor varies considerably,[20,24] therefore an accurate diagnosis is essential.

High-grade glioma cells invade beyond the grossly appreciable tumor margins. This migration of cells is along white matter and blood vessels,[5] ependymal lining, and cerebrospinal fluid spaces.[2] This intracerebral invasion is the major reason for the morbidity associated with these high-grade lesions and is thought to be associated with worse prognosis. The molecular and cellular interactions underlying this invasion have been a matter of extensive debate. Several extracellular proteins such as fibronectin, laminin, tenascin, and collagen IV have been showed to be involved in the spread.[3] Greater infiltrative potential high-grade glioma cells have been supported by studies demonstrating that high-grade glioma cells travel faster compared to low glioma cells along extracellular matrix and proteins.[8,25] Considering the evidence achieved through multiple studies high-grade gliomas are expected to involve ependymal lining of ventricles earlier and more often compared to low-grade gliomas and other lesions.

Imaging characteristics such as degree of contrast area, tumor necrosis volume, and edema surrounding tumor have been well-identified as prognostic markers in high-grade lesion.[7,9,11,23] The diagnostic value of ependymal enhancement (EE) has not studied extensively. In this study, we assess the diagnostic value of EE in differentiating primary high-grade glioma from low-grade gliomas of the brain and non-glioma pathologies.

MATERIALS AND METHODS

This was a retrospective diagnostic study conducted at our institution from 1st January 2013 to 31st December 2015. The review period was from 1st March 2016 to 31st May 2016. The Aga Khan University.

Participants
We included consecutive patients undergoing surgery for space occupying lesions of the brain with preoperative magnetic resonance imaging (MRI) brain available in hospital records for the review and definitive histopathology reports. Patients with inconclusive histopathology reports and missing preoperative MRI scans were excluded from the study. Patient selection is shown in Flowchart 1.

Test method
Preoperative 1.5T MRI scans were reviewed for EE. T1-weighted (T1W) non-enhanced axial images were compared to corresponding T1W contrast enhanced axial images on picture archiving and communication system (PACS). Enhancement of the ependymal lining
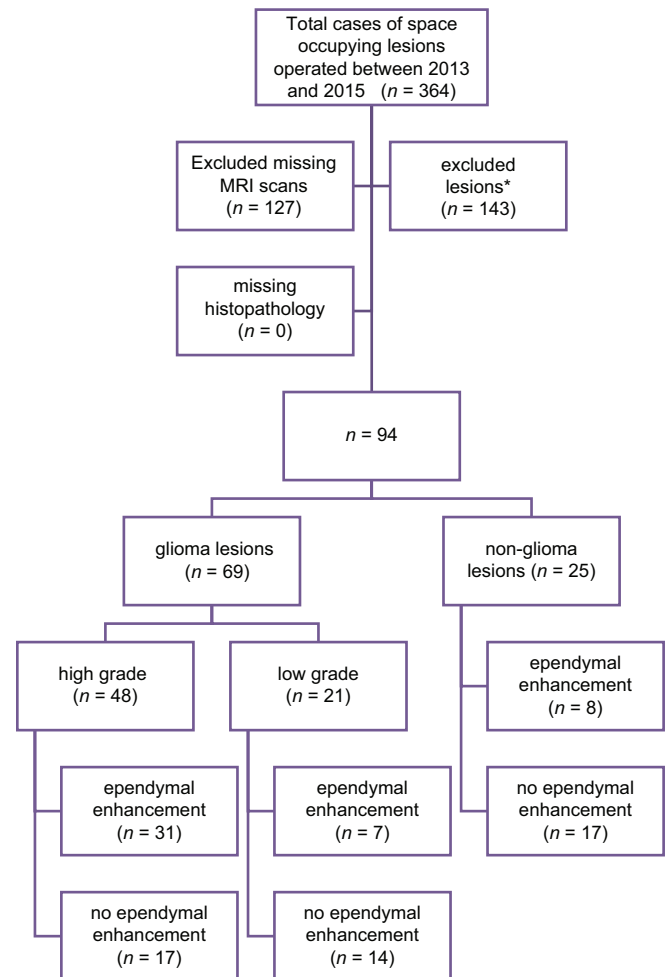
Flowchart 1: Patient selection

more than 2 mm was considered positive. An example of this method is given in Figure 1. MRI were reviewed by a senior neurosurgeon and a neuroradiologist independently, and conflict of opinion was resolved by mutual discussion or by involving a third author. Another author recorded the histopathological diagnosis of these patients unaware of radiological findings. The pathological analysis was performed by a consultant histopathologist who was impartial to study, using World Health Organization (WHO) classification 2016.[14] Glial tumors with (WHO) grade I and II were classified as low grade. MRI were labelled EE positive or negative, and matched with pathological diagnosis.

Statistical analysis
Data was analyzed using IBM SPSS Statistics Version 20 (Chicago, Illinois). Descriptive analysis was done for demographic data. Frequencies and proportions of different pathologies and radiological characteristics were calculated. The sensitivity, specificity, positive, and negative predictive value were calculated by using a 2×2 contingency table. Statistical analysis was done using Pearson Chi-square test. P value was calculated and $P < 0.05$ was considered

significant. Univariate and multivariate logistic regression analysis was applied including variables of age, gender, and EE. Cohen kappa (Cohen K) value was calculated to assess the inter-rater agreement.

RESULTS

Ninety-four patients were included in the study. Of a total of 94 cases, 64 were males and 30 females with a mean age of 44.4 ± 15.75. The procedures included 13 neuronavigation-guided biopsies, 58 craniotomies with excision of lesion, and 23 neuronavigation guided biopsy with excision.

69 gliomas and 25 non-glial lesions were identified [Table 1]. Out of the 69 glioma cases 50 (72.5%) were male. In non-glial cases 14 (56%) out of 25 were male.

Glial vs. non-glial lesions

EE was identified in 38 (55.07%) cases in glial cases and 8 (32%) in non-glioma cases (*P* value 0.048) [Figure 2]. The sensitivity of EE was 82.61% (95% CI: 68.57% to 92.16%), specificity 35.42% (95% CI: 22.17% to 50.54%).

The positive predictive value was 55.07% (95% CI: 42.62% to 67.07%) and a negative predictive value of 68.00% (95% CI: 46.50% to 85.01%). Positive likelihood ratio was 1.28 (95% CI: 1.00 to 1.64) and the negative likelihood ratio was 0.49 (95% CI: 0.24 to 1.03). Diagnostic odds ratio (OR) = 2.61.

High-grade glial vs. all other lesions

Out of the total 48 high-grade lesion 64.58% showed EE, compared with 32.60% in other lesions, *P* value of 0.002 [Figure 3]. The sensitivity of EE in identifying high-grade lesions from all other lesions was 67.39% (95% CI: 51.98% to 80.46%), with a specificity of 64.58% (95% CI: 49.46% to 77.83%). The positive predictive value was 64.58% (95% CI: 49.46% to 77.83%), negative predictive value of 67.39% (95% CI: 51.98% to 80.46%)

positive likelihood ratio of 1.90 (95% CI: 1.24 to 2.93), and a negative likelihood ratio of 0.50 (95% CI: 0.32 to 0.80). These statistics are shown in Table 2. Diagnostic OR: 3.732.

According to univariate analysis OR for EE as a predictor of high-grade glioma was 0.30.6 (95% CI = 0.134 to 0.702, *P* value 0.005). On multivariate regression analysis including variables of age and gender, EE was an independent predictor of a high-grade pathology with an OR of 0.34 (95% CI = 0.144 to 0.810, *P* value = 0.05). OR of EE as a predictor of glial neoplasm was however, not statistically significant with OR = 0. 559 (CI = 0.21 to 1.43, *P* value = 0.228). Cohen k value for inter rater agreement was 0.89 with standard error of 0.45.
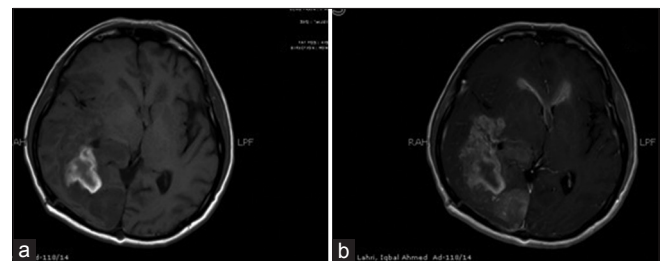

Figure 1: MRI Brain T1W axial non-contrast enhanced (a) and contrast-enhanced image (b) showing heterogeneously enhancing space occupying lesion with distant enhancement of walls of the bilateral frontal horns
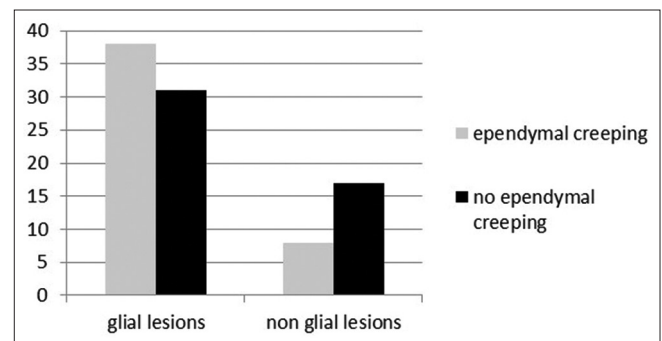
Figure 2: Ependymal enhancement in differentiating glial and non-glial lesions
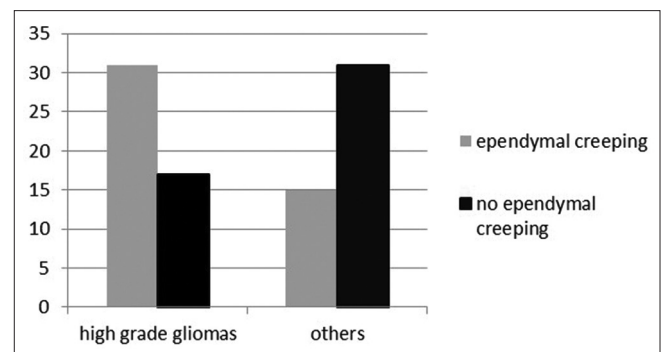
Figure 3: Ependymal enhancement in differentiating high-grade gliomas from other lesions

Table 1: Characteristics of study population

Variable	Number *n* (%)/Mean±SD
Gender	
Male	64
Female	30
Age: Years (Mean±SD)	44±15.75
Gliomas	69
Low-grade gliomas	21
High-grade glioma	48
Non-glioma lesions	25
Metastasis	10
Abscesses	2
Lymphomas	3
Inflammatory lesions	6
Others	4

Table 2: Summary of sensitivity, specificity, PPV, NPV, positive likelihood ratio, and negative likelihood ratio

EE	Glioma vs. non-glioma		High grade vs. other lesions	
	%/Ratio	95% confidence interval	%/Ratio	95% confidence interval
Sensitivity	82.61%	68.57-92.16%	67.39%	51.98-80.46%
Specificity	35.42%	22.17-50.54%	64.58%	49.46-77.83%
Positive predictive value	55.07%	42.62-67.07%	64.58%	49.46-77.83%
Negative predictive value	68.00%	46.50-85.01%	67.39%	51.98-80.46%
Positive likelihood ratio	1.28	1.00-1.64	1.90	1.24-2.93%
Negative likelihood ratio	0.49	0.24-1.03	0.50	0.32-0.80%

PPV: Positive predictive value, NPV: Negative predictive value

DISCUSSION

The usual presentation of gliomas on MRI scans include hypo or iso-intensity on T1W imaging and hyperintensity on T2 imaging.[19] There may be surrounding vasogenic edema, necrotic areas, and distortion of adjacent structures.[1] Computer-extracted MRI features, such as major axis length, percentage enhancement of tumor, and T2 FLAIR and tumor volume are used to predict grade and survival of gliomas.[13,15,17] Association of contrast enhancement with tumor grade is however not definite.[16]

Subependymal region has long been considered a common site for tumor invasion. It is one of the several structures in the brain called Scherer's secondary structures where glioma cells tend to migrate.[22] The presence and migration of glioma cells in the subependymal region not only gives a clue to their origin, but is also consistent with the cellular mechanism of migration of glioma cells along fibronectin in extracellular matrix in the subependymal region.[4] The region is also associated with higher rate of recurrence of gliomas.[2]

EE has also been investigated with multiple pathologies such as viral etiology, inflammatory lesions, meningeal carcinomatosis, meningitis, and ventriculitis and very rarely Whipple's disease or sarcoidosis. Nodular periventricular enhancement may be present in central nervous system (CNS) lymphomas or other neoplastic processes.[6] Relation to subventricular zone (SVZ) and EE with noncontiguous glial tumors to the ventricles is an area of developing interest.[26] Role of EE in predicting survival of patients with high-grade glioma has also been studied with contrasting results.[10]

In the light of existing evidence, we decided to assess the value EE on preoperative imaging in determining final pathology. In our experience, EE has a sensitivity of 82.61% and negative predictive value 68% in glioma vs. non-glioma lesions and its absence may be a useful tool in ruling out the possibility of a lesion being a glioma. It is also important to note that none of our patients with infectious pathology showed EE on MRI. In countries, where tuberculosis is endemic many neurologists and neurosurgeons treat patients with enhancing lesions using anti-tuberculosis treatment without cultures or tissue diagnosis.

The Cohen K value was 0.89 which according to interpretation of Cohen K provided by Landis *et al.* indicates excellent agreement.[12] The specificity of EE is greater in identifying high-grade lesions from the rest (67.39%) than for distinguishing gliomas from non-gliomas (35.42%). The presence of EE greatly increases the index of suspicion and significantly points towards a high-grade lesion (P value = 0.002). OR for EE as an independent predictor of a high-grade pathology was 0.34 (95% CI = 0.144 to 0.810, P value = 0.05). Absence of EE; however, does not rule out presence of tumor cells in the subependymal region since only the areas with neovascularization show contrast enhancement.[21]

We found that the frequency of EE is significantly higher in high-grade gliomas yet it is not an exclusive attribute of higher grade. Number of cases with EE in non-glial lesion and low-grade glioma group though smaller (32% and 33.33% respectively), is not negligible. Therefore, feature of EE fails to achieve near 100% sensitivity and specificity.

To best of our knowledge this is the first study that specifically tries to evaluate EE in distinguishing high-grade glial neoplasms. Preoperative MRI scans and histopathology reports were reviewed independently. To minimize bias reviewers were kept blind to the histopathology reports and features of MRI images. All MRI scans were obtained from one institution and the MRI protocols were uniform and conducted on the same MRI machine.

The study has several limitations. It has a retrospective design. The sample size was limited as a significant number of cases could not be included in the final analysis because of unavailability of preoperative scans at the time of review, primarily due to scans being generated outside the institution. Different patients presented at different times from the onset of symptoms there were at different stage of disease which could affect the presence or absence of EE. A follow-up MRI and overall survival, where possible, could answer the question of ependymal

involvement with disease progression. Further studies need to be done regarding use of EE to assess grade, disease prognosis, multicentricity, recurrence, and detect change in grade on recurrence of a previously low-grade lesion.

CONCLUSION

EE has moderate sensitivity and specificity for high-grade gliomas. However, larger sample studies are required for further validation of these observations.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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