

Use of Preoperative Ependymal Enhancement on Magnetic Resonance Imaging Brain as a Marker of Grade of Glioma

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ABSTRACT

Objectives: Neural stem cells within the subventricular zone (SVZ) are thought to be responsible for the origin and the heterogeneous nature of the gliomas. The relationship of the gliomas to the SVZ can be appreciated as ependymal enhancement on contrast magnetic resonance imaging (MRI). This study evaluates the rate of ependymal enhancement and its association with the histopathological grade of gliomas. **Patients and Methods:** Seventy-five patients with radiological features of glioma were recruited. Preoperative MRI was evaluated for the presence of ependymal enhancement and fluid-attenuated inversion recovery (FLAIR) signal proximity of tumor to ependyma, and the association to grade was investigated. **Results:** Seventy-five patients studied showed a male predominance (62.66%) with a mean age of 44.91 ± 13.64 years. Evidence of ependymal enhancement was positive in 24% ($n = 18$), 46.67% ($n = 35$) showed no evidence, and in 29.33% ($n = 22$), assessment was inconclusive. According to WHO grading, 76% ($n = 57$) were high-grade gliomas (HGGs) including Grade III ($n = 17$) and Grade IV ($n = 40$) and 24% ($n = 18$) were low-grade gliomas (LGGs) Grade II. HGGs were significantly associated with ependymal enhancement ($P < 0.01$) and FLAIR signal proximity to the ependyma ($P < 0.001$). Among HGGs, rate of ependymal enhancement and FLAIR signal proximity was more in Grade IV than Grade III but was not statistically significant ($P > 0.05$). **Conclusion:** SVZ is associated with HGGs. These MRI features can be helpful in predicting the tumor grade preoperatively and by including LGGs, the role of SVZ in the heterogeneous disease process of glioma can be studied as a whole, not only in the glioblastoma (GBM).

KEYWORDS: Ependymal enhancement, fluid-attenuated inversion recovery, glioma, grading, magnetic resonance imaging, neural stem cells, subventricular zone

INTRODUCTION

The adult human brain harbors astrocyte-like neural stem cells (NSC) within the subventricular zone (SVZ), which is located just under the ependyma of the lateral ventricles and subgranular zone of dentate gyrus.^[1-3] In animal models, gliomas – including glioblastoma (GBM) – can be induced from SVZ cells.^[1] These data thus support the notion NSCs proliferate in the SVZ and are responsible for origin of gliomas.

Gliomas are heterogeneous, highly invasive primary brain lesions, and the grade of tumor plays a key role in determining treatment strategies. The primary treatment

of low-grade gliomas (LGGs) is surgical excision. High-grade gliomas (HGGs) include Grade III and Grade IV tumors and require multimodality treatment. Response of HGGs to the treatment, especially of GBM, is highly variable. Heterogeneity may be related to the cells of origin in SVZ.^[4] Magnetic resonance imaging (MRI) is commonly utilized as a part of the diagnostic workup for the clinical diagnosis and treatment planning of

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gliomas.^[5-7] The current study was designed to test the rate of ependymal enhancement and fluid-attenuated inversion recovery (FLAIR) signal proximity of tumor to ventricular ependymal in preoperative MRI as a marker of grade and behavior of glioma to assess the relationship of the glioma with SVZ.

PATIENTS AND METHODS

Seventy-five patients with radiological features suggestive of supratentorial glioma, who were treated at our institution from December 2015 to December 2016, were included in the study. Ethical clearance from the Institutional Ethical Committee was obtained. Patients were included in the study if their contrast-enhanced MRI was suggestive of gliomas. Patients with posterior fossa lesions, any systemic malignancy, inadequate imaging, and histopathology other than gliomas were excluded from the study. Data recorded included the age of the patient, date of diagnosis, Karnofsky performance score (KPS) at the time of first visit, comorbidities, symptoms, any drug or contrast allergy, and MRI findings. Tumor grade was histologically confirmed in all cases in the Department of Pathology at our institution.

Most of the patients underwent the same preoperative MRI protocol, which consists of T1 fast field echo (FFE) (222/4.6 [TR/TE]), an axial sagittal and coronal T2W Turbo spin echo (2500/80 [TR/TE]), axial FLAIR sequence (10000/125/2800 [TR/TE/TI]), axial diffusion-weighted imaging (TR/TE [2540/91]), and a postcontrast FFE T1. All MRI studies were reviewed by an experienced radiologist blinded to patient treatment protocols and histopathology. Tumors were classified as contrast-enhancing lesion bordering the ependyma and contrast-enhancing lesion not bordering the ependyma, and FLAIR signal proximity to the ependymal surface present or absent.

Based on ependymal enhancement on contrast MRI, cases were divided as follows - with evidence of ependymal enhancement present, ependymal enhancement absent, assessment of ependymal enhancement inconclusive due to mass effect, and ventricular compression that precluded accurate assessment. The last group was not used in calculations of ependymal enhancement. Based on FLAIR signal proximity to ependyma, cases were divided into two groups whether it was present or absent.

Histopathological grades of all the patients were examined, and grade of gliomas was seen with respect to the presence or absence of ependymal enhancement and with respect to FLAIR signal proximity to ependymal surface.

Statistical analysis

Data were analyzed using statistical software package SPSS Inc. Released 2007 and SPSS for Windows, version 16.0, SPSS Inc., Chicago, IL, USA. The qualitative data were analyzed using Chi-square test. The quantitative data were analyzed by Z-test. $P < 0.05$ was considered statistically significant.

RESULTS

In the present study, 75 cases of supratentorial gliomas with ages ranging from 12 to 75 years (mean age of 44.91 ± 13.64 years) were studied. Males were affected more ($n = 47$) than females ($n = 28$). Headache was the most common symptom, present in 69.33% ($n = 52$) cases followed by weakness 34.6% ($n = 26$). Seizures were present in 28% ($n = 21$) with generalized tonic-clonic in 25.33% ($n = 19$) and partial seizure in 2.67% ($n = 2$). Vomiting was present in 25.33% ($n = 19$). Eight percent ($n = 6$) of patients had difficulty in speech with 6.67% ($n = 5$) having motor aphasia and 1.33% ($n = 1$) with slurred speech, consciousness was altered in 13% ($n = 10$), and cranial nerve involvement was present in 4% ($n = 3$).

Karnofsky Performance score (KPS) was ≥ 70 in 70.67% ($n = 53$) patients and < 70 in 29.33% ($n = 22$). Hypertension was the most common comorbidity, present in 18.67% ($n = 14$), followed by diabetes in 10.67% ($n = 8$) and chest infection in 1.33% ($n = 1$).

According to WHO grading, 18 (24%) cases were of Grade II, 17 (22.67%) of Grade III, and 40 (53.33%) were GBM-Grade IV. Grade III and Grade IV were high grade and Grade I and Grade II were low grade. There was no Grade I case in the study. Mean \pm standard deviation (SD) age was 39.39 ± 12.07 years for Grade II ($n = 18$), 40.18 ± 13.41 years for Grade III ($n = 17$), and 49.40 ± 12.79 years for Grade IV ($n = 40$) gliomas [Table 1]. Mean KPS was 82.94 ± 15.25 for Grade II ($n = 18$), 82.94 ± 15.25 for Grade III ($n = 17$), and 70.00 ± 20.73 for Grade IV ($n = 40$) gliomas [Table 2].

Evidence of ependymal enhancement on MRI was present in 24% ($n = 18$) [Figures 1 and 2]. Enhancement

Table 1: Mean \pm standard deviation of age of study subjects according to grade

Grade	n	Mean \pm SD
Grand II	18	39.39 \pm 12.07
Grand III	17	40.18 \pm 13.41
Grand IV	40	49.40 \pm 12.79

Grand II versus Grand III $P > 0.05$ NS, Grand II versus Grand IV $P < 0.05$ S, Grand III versus Grand IV $P < 0.05$ S. NS: Not significant, S: Significant, SD: Standard deviation

was not present in 46.67% ($n = 35$) [Figure 3]. In 29.33% ($n = 22$), assessment was inconclusive [Figure 4 and Tables 3-5].

Flair signal proximity to ventricular ependyma was present in 50.67% ($n = 38$) patients [Figure 5] and absent in 49.33% ($n = 37$) patients [Figure 6]. Among HGGs, 45.61% ($n = 26$) in Grade IV and 19.29% ($n = 11$) in Grade III showed FLAIR signal proximity to ependyma [Tables 6 and 7].

DISCUSSION

Gliomas have been classified by the WHO into four grades. Grade I shows low proliferative potential and the possibility of cure following surgical resection alone. Grade II defines diffusively infiltrative tumors with cytological atypia alone, for example, diffuse astrocytoma. Grade III has atypia, anaplasia, and mitotic

activity, for example, anaplastic varieties of astrocytoma, ependymoma, and oligoastrocytoma. Grade IV tumors additionally show microvascular proliferation and necrosis, for example, GBM.

LGGs are typically hypointense on T1, hyper on T2 relative to white matter, contrast enhancement may be absent or, at best, mild. Grade III astrocytoma often

Table 2: Mean±standard deviation of Karnofsky performance scale of study subjects according to grade

Grade	n	Mean±SD
Grand II	18	82.94±15.25
Grand III	17	72.50±21.36
Grand IV	40	70.00±20.73

Grand II versus Grand III $P > 0.05$ NS, Grand II versus Grand IV $P < 0.05$ S, Grand III versus Grand IV $P > 0.05$ NS. NS: Not significant, S: Significant, SD: Standard deviation



Figure 1: Evidence of ependymal enhancement present. Axial gadolinium-enhanced T1-weighted image showing an enhancing tumor extending along the ventricular wall

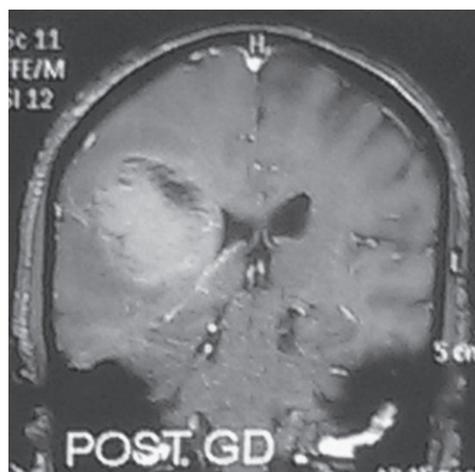


Figure 2: Evidence of ependymal enhancement present. Coronal gadolinium-enhanced T1-weighted image showing an enhancing tumor extending along the ventricular wall



Figure 3: No evidence of ependymal enhancement on magnetic resonance imaging. Axial gadolinium-enhanced T1-weighted image showing a left parietal lesion not contacting the ventricular wall

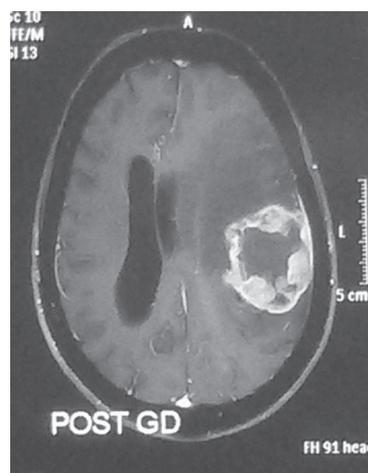


Figure 4: Inconclusive for ependymal enhancement on magnetic resonance imaging. Axial gadolinium-enhanced T1-weighted image showing a ring enhancing lesion on the left side compressing the left lateral ventricle making it impossible to appreciate ependymal enhancement

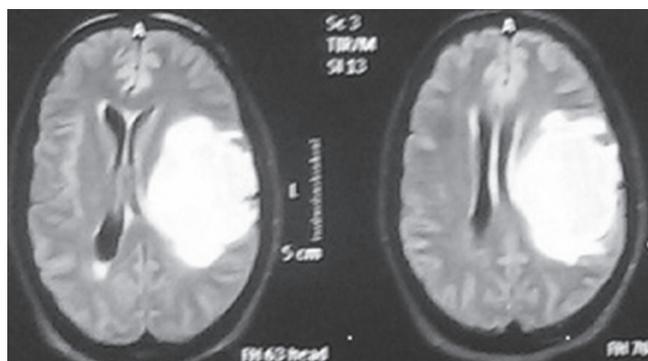


Figure 5: Fluid-attenuated inversion recovery signal proximity to ependyma present

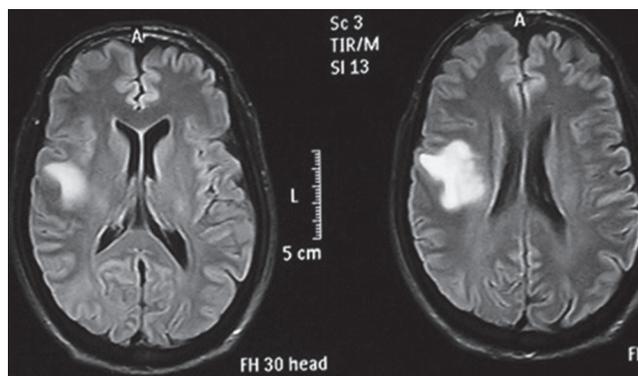


Figure 6: Fluid-attenuated inversion recovery signal proximity to ependyma absent

Table 3: Distribution according to ependymal enhancement in histopathological grade of study subjects

Ependymal enhancement	Biopsy grade		Total
	High grade	Low grade	
Present	17 (22.67)	1 (1.33)	18 (24.00)
Absent	20 (26.67)	15 (20.00)	35 (46.67)
Inconclusive	20 (26.66)	2 (2.67)	22 (29.33)
Total	57 (76.00)	18 (24.00)	75 (100.00)

Table 4: Distribution according to ependymal enhancement in high-grade gliomas and low-grade gliomas

Ependymal enhancement	Biopsy grade		Total
	High grade	Low grade	
Present	17 (32.07)	1 (1.89)	18 (33.96)
Absent	20 (37.74)	15 (28.30)	35 (66.04)
Total	37 (69.81)	16 (30.19)	53 (100)

$\chi^2=6.1777$, $df=1$, $P<0.01$ S. S: Significant

Table 5: Distribution according to ependymal enhancement in Grade III and Grade IV

Ependymal enhancement	Biopsy grade		Total
	Grade III	Grade IV	
Present	5 (8.77)	12 (21.05)	17 (29.82)
Absent	12 (21.05)	28 (49.13)	40 (70.18)
Total	17 (29.82)	40 (70.18)	57 (100.00)

$\chi^2=0.070$, $df=1$, $P>0.05$ NS. NS: Not significant

invade structures without destroying them, causing their ill-defined borders. The mass is inhomogeneous and bright on T2-weighted images. Surrounding edema and/or tumor infiltration is usually appreciated. Enhancement is usually seen. Grade IV tumors (GBM) are usually discovered as bulky disease, and necrosis is a hallmark of this grade. These lesions usually enhance peripherally, in a nodular and irregular manner, and they cause a large amount of mass effect and edema.^[6] These tumors often cross the corpus callosum, giving them a typical butterfly shape. Areas of hemorrhage and necrosis are common.

Treatment of HGGs consists of maximal safe surgical resection followed by radiotherapy (RT) with temozolomide chemotherapy.^[8] GBM carries a poor prognosis with median survival of 12–14 months. Prognosis and response to standard therapy with resection, radiation, and chemotherapy are highly variable suggesting heterogeneous nature of this deadly disease.^[4] Recent evidences show that heterogeneity seen in GBM may be related to the cells of origin, NSCs in SVZ. The SVZ is composed of four layers. Layer 1 is the innermost layer, composed of ependymal cells. Layer 2 contains astrocytic processes connecting ependymal cells with astrocytes.^[3] Layer 3 consists of astrocytic cell bodies that have been implicated as potential sources of multipotent stem cells. Layer 4 has myelin and separates Layer 3 from underlying brain parenchyma. Prior studies suggest that GBM adjacent to the SVZ are more likely to manifest the highly invasive and multifocal phenotype and may be associated with increased recurrence rate and morbidity.^[4,9-13] Hence, this subset of GBM or the gliomas related to SVZ should be treated more aggressively early in their disease from therapy specifically targeting the SVZ.

Patient age, performance status, extent of resection, and chemo-RT are long established prognostic factors in GBM patients.^[14] Research progress on molecular aspect of GBM has revolutionized our understanding of the disease, and it is recently learned that prognosis correlates with molecular characteristics (Hyper methylation of MGMT) of the tumor.^[15] Because it is not practically possible to provide molecular profiling to every patient, we aim to test the association between tumor grade and the proximity to SVZ to further predict the outcome of this deadly disease^[16,17] and to provide a radiological tool in the form of ependymal enhancement.

In our study, based on ependymal enhancement, cases were divided into three groups, with evidence of enhancement, without evidence of enhancement, and

Table 6: Distribution according to fluid-attenuated inversion recovery signal proximity to ependyma in high-grade gliomas and low-grade gliomas

FLAIR signal proximity to ependyma	Biopsy grade		Total
	High grade	Low grade	
Present	37 (49.33)	1 (1.34)	38 (50.67)
Absent	20 (26.67)	17 (22.66)	37 (49.33)
Total	57 (76.00)	18 (24.00)	75 (100.00)

$\chi^2=16.980$, $df=1$, $P<0.001$ S. S: Significant, FLAIR: Fluid-attenuated inversion recovery

Table 7: Distribution according to fluid-attenuated inversion recovery signal proximity to ependyma in Grand III versus Grand IV

FLAIR signal proximity to ependyma	Biopsy grade		Total
	Grade III	Grade IV	
Present	11 (19.29)	26 (45.62)	37 (64.91)
Absent	6 (10.53)	14 (24.56)	20 (35.09)
Total	17 (29.82)	40 (70.18)	57 (100)

$\chi^2=0.080$, $df=1$, $P>0.05$ NS. NS: Not significant, FLAIR: Fluid-attenuated inversion recovery

as inconclusive. This distribution is similar to the one adopted by Kaidar-Person *et al.*^[16] The inconclusive group was not taken into calculations regarding ependymal enhancement.

Glioma tumor grade was significantly associated with ependymal enhancement as, 32.07% ($n = 17$) patients of high grade and only 1.89% ($n = 1$) of low grade showed enhancement ($P < 0.01$). On further analyzing among HGGs, 8.77% ($n = 5$) in Grade III and 21.05% ($n = 12$) in Grade IV had evidence of ependymal enhancement which was not statistically significant ($P > 0.05$). Glioma tumor grade was significantly associated with T2 FLAIR signal proximity to the ventricular ependyma ($P < 0.001$). A total of 50.67% ($n = 38$) patients had T2 flair signal proximity to ependyma, of which 37 (49.33%) were HGGs and only 1 (1.33%) was of low grade. Among HGGs, 45.61% ($n = 26$) in Grade IV and 19.29% ($n = 11$) in Grade III showed FLAIR signal proximity to ependyma which was not statistically significant ($P > 0.05$).

On MRI, GBM has been observed to contain a high frequency of T2-weighted/FLAIR hyperintense regions contiguous with the posterior SVZ.^[17] There are multiple studies show that patients with GBM in contact with SVZ show shorter survival^[9-12] and more aggressive recurrence.^[13] Our results also support that higher grade tumors are more closely linked to the SVZ, as a rate of ependymal enhancement was significantly high in HGGs. Our study also reflects that among HGGs, the rate of ependymal enhancement is more in GBM as

compared to Grade III tumors, but it was not statistically significant. This observation shows that relationship to SVZ also holds good for Grade III tumors. These results are in accordance with prior results as shown by Smith *et al.*^[17]

Our results demonstrate that higher tumor grade is associated with the proximity of MRI T2-weighted FLAIR signal to the ependyma. This observation also suggests that higher grade tumors are closely related to the SVZ. On further analyzing HGGs, T2 FLAIR proximity was more in GBM than Grade III tumors, but it was not statistically significant.

Contrary to this hypothesis, there are studies that failed to show the relationship and showed that pretreatment ependymal enhancement on MRI in GBM was not associated with poor survival.^[16] All these observations make it more interesting and merit further investigation.

While previous studies examined relationship between GBM behavior and SVZ,^[9-13] very few studies have included LGGs.^[17,18] There has been a study of Grade II astrocytoma showing increased tumor volume in tumors adjacent to the SVZ, suggesting that proximity to SVZ may correlate with enhanced proliferative potential^[18] and even LGGs may have association with the SVZ. Our study also included LGGs. Ependymal enhancement was present in only one LGG, and further studies are needed before commenting on relationship of LGG with SVZ.

Analysis of clinical factors (other than ependymal enhancement) to predict tumor grade showed that age and KPS were significantly associated across tumor grades. Mean \pm SD age was 39.39 ± 12.07 years for Grade II ($n = 18$), 40.18 ± 13.41 years for Grade III ($n = 18$), and 49.40 ± 12.79 years for Grade IV ($n = 40$) and was statistically significant ($P < .05$) between Grade II/Grade IV and Grade III/Grade IV. Mean \pm SD KPS was 82.94 ± 15.25 for Grade II ($n = 18$), 82.94 ± 15.25 for Grade III ($n = 17$), and 70.00 ± 20.73 for Grade IV ($n = 40$) and was statistically significant between Grade II and Grade IV ($P < 0.05$). Both these findings were in accordance with the prior studies.^[14]

The merits of our study are that it is a prospective study that attempts to describe the role of preoperative ependymal enhancement with respect to the grade of gliomas. It also includes LGGs so that role of SVZ can be studied across all the grades.

Our study has few limitations. First, it is a relatively small sample size of 75 patients, and of these, in 22 cases, ependymal enhancement was inconclusive for involvement reducing the size further.

CONCLUSION

This study shows that preoperative ependymal enhancement and FLAIR signal proximity to ependyma are associated with HGGs. It can be helpful in predicting the tumor grade preoperatively, and by including LGG in the study, the role of SVZ in the heterogeneous disease process of glioma can be studied as a whole, not only in the GBM. Further studies oriented toward both LGGs and HGGs are needed to see the utility of ependymal enhancement and whether it can be established as a radiological tool to predict the grade so that more intensive therapeutic options can be applied to this subset of patients and better results in terms of tumor-free period and survival can be obtained.

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Conflicts of interest

There are no conflicts of interest.

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