Role of Quantitative Apparent Diffusion Coefficient in Predicting Genetic Subtypes of Gliomas

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Abstract

Introduction: Magnetic resonance morphologic features are widely used in characterising gliomas for predicting grades and thereby aiding in preoperative management planning. We aim to find out if Magnetic Resonance Imaging morphologic characters and quantitative apparent diffusion coefficient (ADC) measurements can predict genetic subtypes of high-grade gliomas.

Methods and Materials: Preoperative MRI examinations of histopathologically proven gliomas were retrospectively studied for qualitative tumor characteristics, including location, extent, cortical involvement, margin sharpness, cystic component, mineralization or hemorrhage, and contrast enhancement. Quantitative diffusion metrics were also assessed. Chi-square test, students t-test and multivariate regression analysis were used to evaluate the relationship between MRI features and *IDH* mutational status.

Results: The final study population included 23 patients (16 males and seven females, mean age 40 years ± 14.4, age range 13–66years). Nine tumors were *IDH* mutant and 14 were *IDH* wild type. *IDH* wild-type tumors showed patchy to diffuse diffusion restriction and a lower apparent diffusion coefficient (ADC) compared to IDH mutant types. T2/FLAIR high signal and maximum ADC values were associated with *IDH* mutational status. Contrast enhancement, hemorrhage and necrosis were significantly higher in IDH wild type gliomas. There was no statistical difference in the age, gender, tumor burden, location, site and edema between the IDH-mutant and wild-type tumors.

Conclusions: MR morphometric parameters that include T2/FLAIR signal character, contrast enhancement pattern, hemorrhage and necrosis and Quantitative mean ADC /normalized ADC can support preoperatively the distinction of genetic subtypes of gliomas.

Key words: apparent diffusion coefficient, genetic subtypes, glioma, magnetic resonance morphology

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Introduction

The traditional histopathology analysis of tumors includes proliferative and mitotic activity, nuclear atypia and cellularity as significant predictors of disease grade and progression.[1,2] More than 90% of glioblastomas belong to the IDH wild-type group.[3,4] Mutations in isocitrate dehydrogenase (IDH) represent a common (> 70%) defining event in the development of LGG. Isocitrate dehydrogenase (IDH) mutation is currently implicated as a prerequisite of tumorigenesis for some types of diffuse gliomas and a precondition of 1p/19q co-deletion.[3,4] According to the 2016 WHO classification system, the integrated diagnosis of gliomas requires histological classification, WHO grade, and molecular information (both IDH mutation and 1p/19q co-deletion).[5] WHO grade II/ III gliomas have three molecular subgroups, viz: IDH wild-type glioma (IDH^{wt}) with survival similar to that of glioblastoma, IDH-mutant glioma with intact 1p19q ($IDH^{mut}1p19^{int}$) and an intermediate prognosis, and IDH

mutant 1p19q co-deleted glioma ($IDH^{mut}1p19^{del}$) with the best prognosis and greatest chemosensitivity.[4]

Diffusion-weighted imaging (DWI) reflects the Brownian movement of water molecules and the cytogenetic profile of cerebral tumors through the measurement of apparent diffusion coefficient (ADC) values. [6] DWI has contributed to a great deal in cancer management. Water diffusivity is impaired in highly cellular tissues reflecting tumor proliferative rate and aggressiveness. Quantitative apparent diffusion coefficient (ADC) values have demonstrated high accuracy for glioma grading through meta-analysis.[7] For the non-invasive identification of low to intermediate IDH^{wt} glioma, diffusion tensor imaging (DTI) and diffusion kurtosis imaging (DKI) have shown potential, suggesting that reduced and heterogenous diffusivity are IDH^{wt} features.[9,10,11] As recently revealed, IDH mutations or 1p/19q codeletions correlate with aberrant cellularity and angiogenesis by regulating proliferation and vascularization.[8,9]

During the past two decades, extensive studies have focused on the surrogate MRI characters of histopathologic tumor grades and genetic subtypes of CNS tumors.[8,9,10,11]

To our knowledge, there are very few advanced MRI studies in pre-surgical grading of the redefined tumors.

Therefore, the present study aims to find out whether MRI morphologic parameters and ADC measurements from routine DWI study are predictive of glioma molecular subtype

Methods and Materials

Patient Cohort

23 consecutive patients diagnosed with primary gliomas between January 2017 and March 2018, who underwent MRI as part of the pre-surgical workup were retrospectively examined. The inclusion criteria were (1) a histopathology diagnosis of glioma according to 2007 WHO classification; (2) 1.5 Tesla conventional MRI scans combined with DWI and SWI followed by contrast study before any intervention; and (3) a known IDH mutation and 1p/19q co-deletion status for reclassification according to 2016 WHO guidelines. Morphological characters of tumors assessed in conventional MRI included origin and laterality of tumor with tumor burden at the time of presentation, signal characteristics in T1WI, T2WI and FLAIR, associated degree of parenchymal edema, hemorrhage and necrosis and enhancement pattern post gadolinium-based contrast agent. Quantitative assessment of the diffusion restriction was assessed with absolute mean and normalized ADC values. General exclusion criteria were any contraindications to MRI exams, and agitated or non-cooperating patients.

The histopathologic diagnosis was made by experienced neuropathologist according to the updated WHO classification standards. Tumor diagnosis was based on histological examinations of surgical specimens, aided by immunohistochemical testing for known biomarkers (ATRX, IDH1, p53, EGFR) and molecular tests for IDH 1 mutations and 1p/19q co-deletion.

The institutional review board approved the study. All patients provided written informed consent for the imaging surveys and the subsequent use of images for scientific and research purposes.

Image acquisition

All exams were performed at a 1.5 Tesla MRI scanner (Magnetom Essenza, Siemens Healthineers, Erlangen, Germany). The conventional MR examination protocol included high-resolution T2 and FLAIR and T1-weighted sequences before and after gadolinium administration (Magnavist®; Bayer-Schering, Germany). Spin-echo, echo-planar imaging DWI sequence was acquired with the following parameters: b-values included 0, 90, 1000 sec/mm2 for each b-value diffusion encoding; TR 3900 ms; TE 111 ms; field of view 230 Å~ 230 cm2; matrix 128 Å~ 128; bandwidth, 1055 Hz/pixel; slice thickness, 5 mm; number of signal averages, 3; The total time of the DWI acquisition was 1 min 23 s.

In a spin echo diffusion-weighted sequence, the signal $\mathbf{S}_b$ [$\mathbf{S}_b = \mathbf{S}_0\ e^{(-b\ ADC)}$] from each pixel in an image is formed of a first component ($\mathbf{S}_0$) dependent on tissue properties (i.e. 'spin density', T_1 and T_2 relaxation times) and sequence properties (e.g. repetition time, TR); and a second component ($e^{-b\ ADC}$) dependent on the diffusion gradients (*b*, in units of s/mm^2) and the apparent diffusion coefficient (ADC, in units of mm^2/s).

The ADC is obtained by dividing the image acquired without diffusion gradients ($\mathbf{S}_{b=0}=S_0$) by the image acquired with diffusion gradients ($\mathbf{S}_b$): $ADC = (1/\mathbf{b})\ ln\ (\mathbf{S}_0/\mathbf{S}_b)$

ADC was measured selecting two round regions of interest on the ADC map viewed side-by-side: The first region of interest (ROI) was drawn in the largest solid component of the lesion excluding necrosis and hemorrhage if any present and sparing the tumor margin to avoid partial volume effects. The second round ROI was taken in contralateral centrum semi-ovale (CS) excluding ventricular surfaces, cortex and sulci. The ratio between the ADC_{mean} in the tumor and CS was calculated as Normalized ADC (NADC).

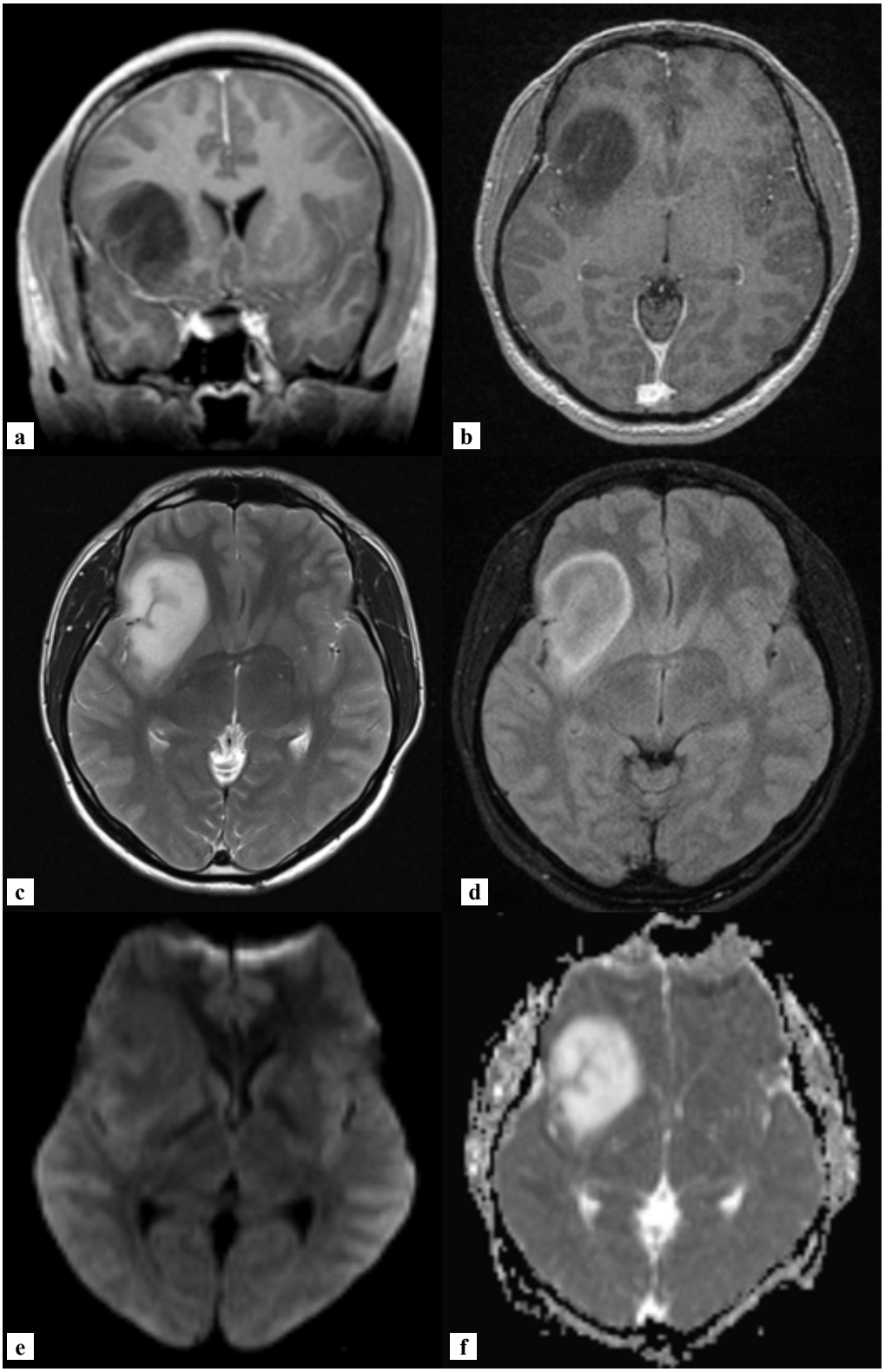

Figure 1.a-f. 30 years male with IDH mutant right peri sylvian diffuse astrocytoma. T1W coronal image (a) shows well demarcated hypointense signal mass in right peri sylvian region. Post gadolinium axial T1WI (b) shows no contrast enhancement. Corresponding T2WI (c) shows fairly marginated lesion with homogenous high signal demonstrating partial suppression of T2 high signal representing relatively high water content in axial FLAIR image (d) No significant perifocal edema is seen. DWI (e) shows no diffusion restriction ADC map(f) shows bright signal with high ADC value.

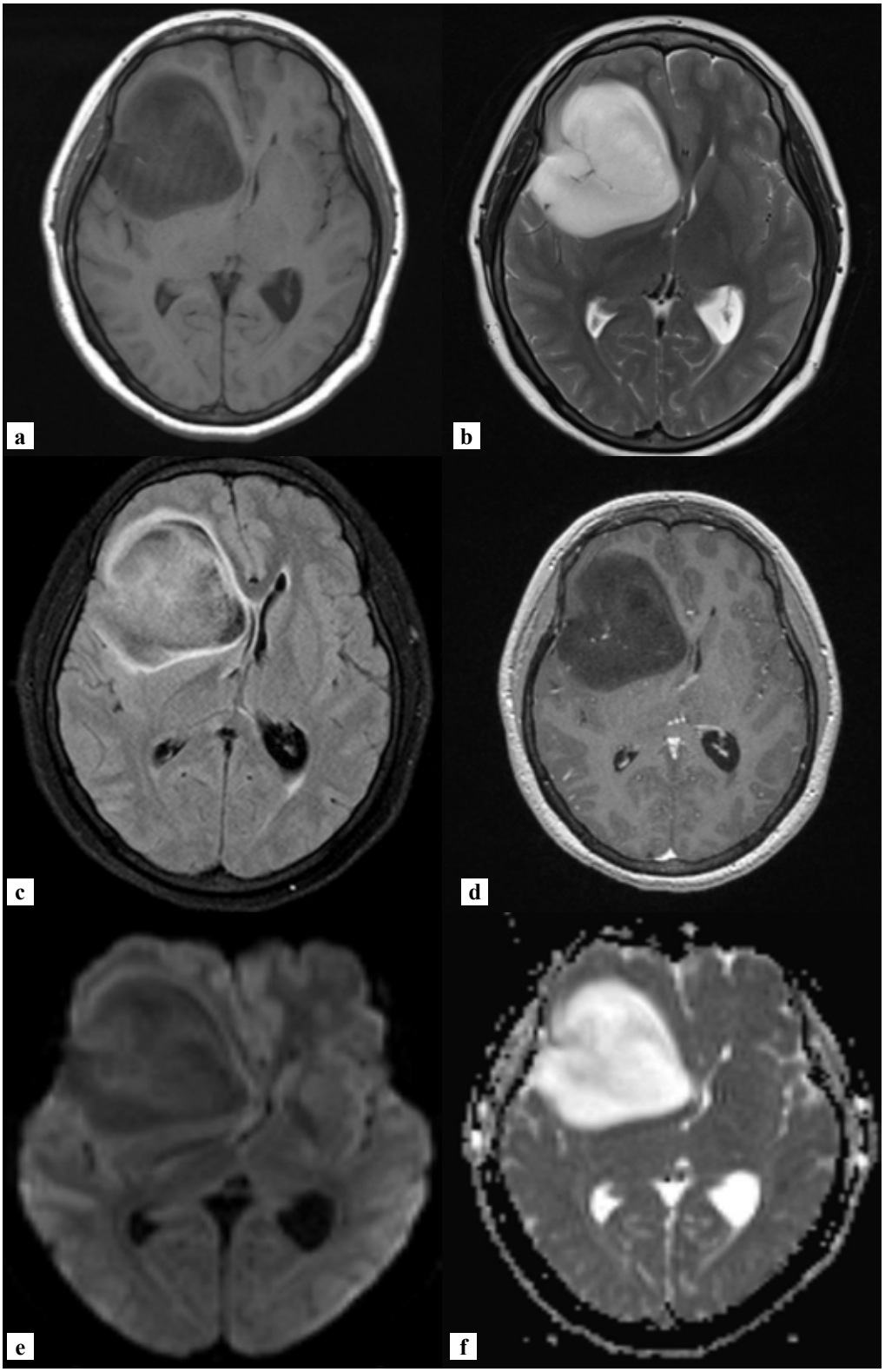

Figure 2 a-f. 25 years female with IDH mutant right perisylvian astrocytoma displays similar MR features as fig 1. Axial section T1WI (a) shows well marginated large right perisylvian mass showing some mass effect over right frontal horn and subtle subfalcine herniation. Corresponding axial T2WI (b) shows homogenous high T2 signal partly suppressed in FLAIR axial section(c) with peripheral rim of edema. Post gadolinium axial T1WI (d) shows no enhancement of the lesion. DWI (e) shows no diffusion restriction. Corresponding ADC map (f) shows high signal with high ADC value

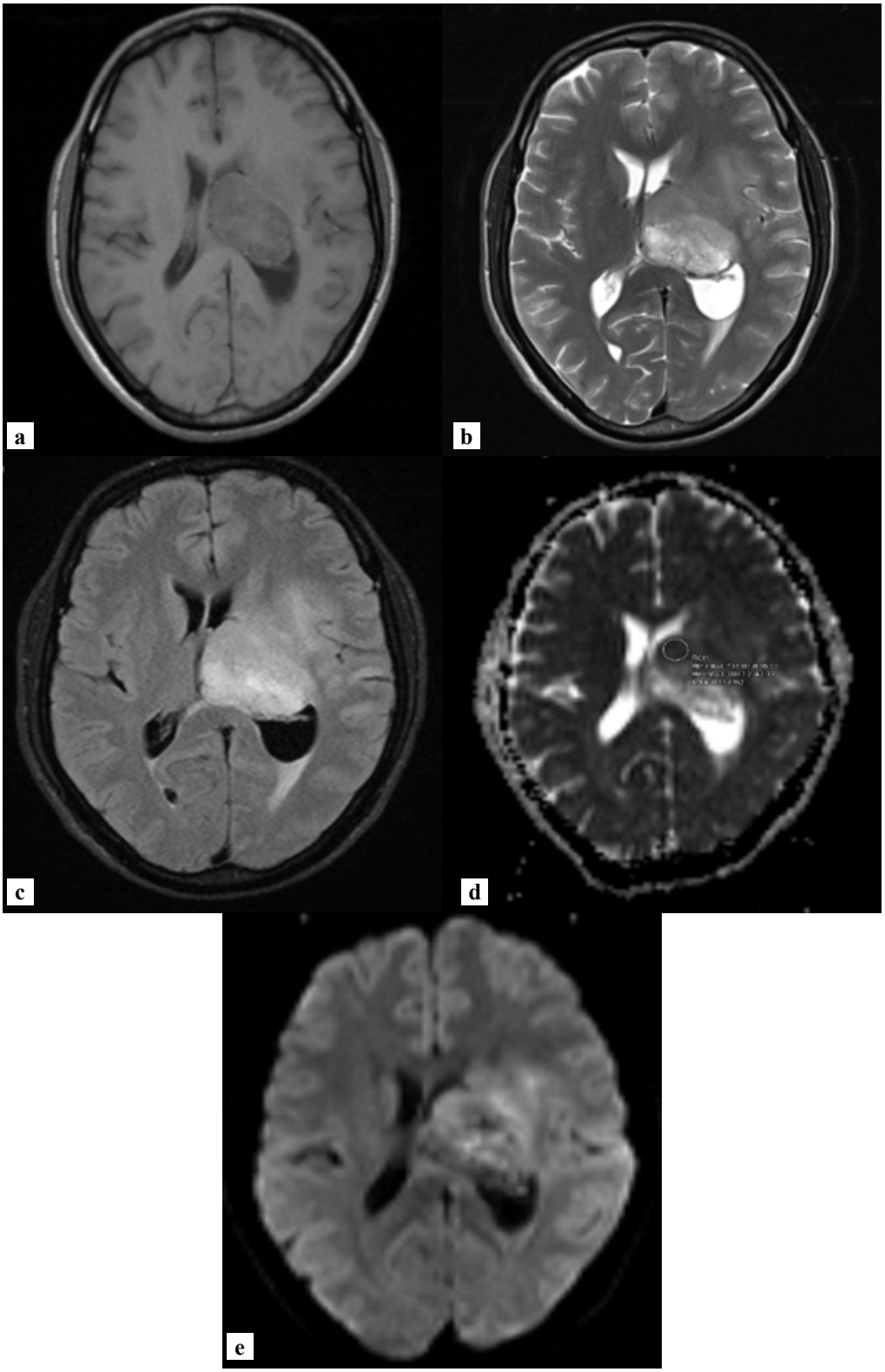

Figure 3 a-e. 36 years male with IDH wild type thalamomesencephalic astrocytoma. (a) Axial T1WI shows poorly marginated isointense mass in left thalamus. Corresponding axial T2WI (b) shows heterogeneous high signal lesion with minimal perifocal edema and mild dilatation of left occipital horn. FLAIR image (c) shows heterogenous signal with mild edema. DWI (d) demonstrates diffusion restriction in solid portions of the lesion with low signal with low ADC value of the mass in ADC map (e).

Results

A total of 23 patients with Gliomas were evaluated. Mean age was 40.04 ±14.4 years with age range of 13 to 66 years with 16 males and seven females making male female ratio of 2.3. Mean tumor burden at the time of presentation was 38+/-22.4 cc.

13 (56.5%) tumors were right sided, nine (39.1%) were left sided and one was butterfly glioma. Majority (22, 95.7%) tumors were supra-tentorial and one (4.3%) was infra-tentorial. Most of the tumors (19, 82.6%) were lobar whereas four (17.4%) tumors were located in thalamo-mesencephalic region.

16 patients with WHO grade IV, three patients with WHO grade III, four patients with WHO grade II tumors were found by immunohistochemistry study. Among WHO grade II Gliomas, three were diffuse astrocytoma and one was central neurocytoma.

14 (61%) of the tumors were IDH wild ATXR wild type and 9 (31%) tumors were IDH mutant and ATXR wild.

Majority of the tumors showed heterogeneous signal intensity in all MRI sequences. However, most of the IDH mutant tumors showed significantly increased signal in T2WI (p=0.001) and FLAIR sequences (p=0.009) compared to IDH wild type. This mismatch of signal between T2 and FLAIR sequences seen in IDH mutant tumors was an important and interesting finding. Hemorrhage was present in 18 of the tumors whereas necrosis was present in 14 of the tumors. Likewise, hemorrhage and necrosis were significantly high in IDH wild type of gliomas with p value of 0.034 and 0.03 respectively. IDH wild type gliomas showed higher moderate to avid enhancement with gadolinium compared to IDH mutant gliomas, which was statistically significant (p=0.001).

Nine (39.1%) of the tumors showed patchy areas of diffusion restriction corresponding to contrast enhancing solid portions of the tumors whereas nine (39.1%) of the tumors also showed facilitated diffusion. Majority of the tumors showing facilitated diffusion had either no enhancement to minimal patchy enhancement post gadolinium.

Mean ADC of the solid component of the overall tumors was $0.957 \pm 0.408 \times 10^{-3}$ mm^2/s with mean reference ADC of centrum semi-ovale was $0.777 \pm 0.54 \times 10^{-3}$ mm^2/s. There was highly significant difference in absolute mean ADC between the two groups with lower ADC in IDH wild type tumors ($0.713 \pm 0.132 \times 10^{-3}$mm^2/s) and higher ADC in IDH mutant type ($1.337 \pm 0.41 \times 10^{-3}$ mm^2/s) with a p value of 0.000024 (Table 1).

Mean NADC value of IDH wild type gliomas was 0.9134±0.198 and that of IDH mutant type was 1.729 ± 0.425 (p=0.000024). Normalized ADC of less than one representing diffusion restriction was significantly high in Grade IV gliomas than in lower grades gliomas. In addition, NADC of less than one was significantly higher in IDH wild type than in IDH mutant type gliomas (p=0.00023). Tumors with diffusion restriction showed significant correlation with necrosis whereas no significant correlation was found with hemorrhage and calcification (Table 1).

VARIABLES		Total N=23	IDH-WT n=14 (60.86%)	IDH-MT n=9 (39.14%)	P VALUE
AGE	Mean±SD	40.04+14.427	39.19±18.09	36.2±29.11	0.763
SEX	M	16 (69.6%)	8 (57.1%)	8 (88.8%)	0.106
	F	7 (30.4%)	6 (42.9%)	1 (4.34%)	
T1W	Hypo	9 (39.1%)	4 (17.4%)	5 (21.7%)	0.350
	Iso	5 (21.7%)	3 (13%)	2 (8%)	
	Mixed	9 (39.1%)	7 (30.4%)	2 (8%)	
T2W	Hyper	10 (43.4%)	2 (8%)	8 (34.7%)	0.001
	Mixed	13 (56.5%)	12 (52.1%)	1 (4.34%)	
FLAIR	Iso	2 (8%)	0	2 (8%)	0.009
	Hyper	5 (21.7%)	1 (4.34%)	4 (17.4%)	
	Mixed	16 (69.5%)	13 (56.5%)	3 (13%)	
EDEMA	Minimal	10 (43.4%)	6 (26%)	4 (17.4%)	0.94
	Marked	13 (56.5%)	8 (34.7%)	5 (21.7%)	
HEMORRHAGE	Absent	5 (21.7%)	1 (4.34%)	4 (17.4%)	0.034
	Present	18 (78.2%)	13 (56.5%)	5 (21.7%)	
NECROSIS	Absent	9 (39.1%)	3 (13%)	6 (26%)	0.03
	Present	14 (60%)	11 (47.8%)	3 (13%)	

CALCIFICATION	Absent	17 (73.9%)	10 (43.4%)	7 (30%)	0.735
	Present	6 (26%)	4 (17.4%)	2 (8%)	
CONTRAST ENHANCEMENT	Absent	2 (8%)	0	2 (8%)	0.001
	Minimal	7 (30%)	1 (4.34%)	2 (8%)	
	Moderate	9 (39.15%)	9 (39.1%)	6 (26%)	
	Avid	5 (21.7%)	4 (17.4%)	1 (4.34%)	
TUMOR VOLUME	Mean±SD	38.02±22.44	39.86±15.88	40.33±12.748	0.535[t]
NADC	<1		11	0	0.000232
	≥1		3	9	
ADC ($10^{-3}mm^2/s$)	Mean±SD	0.96±0.41	0.713±0.132	1.337±0.41	0.000024
NADC	Mean±SD	1.23±0.50	0.9134±0.198	1.729±0.425	0.000024

Note P 0.000024, comparing average ADC/NADC of Group A (IDH-Wild) vs Group B (IDH- mutant) by use of Student's two-tailed t test.

Table 1: Comparative Study of Variables between IDH-Wild and Mutant Types

Discussion

Gliomas are a diverse group of CNS neoplasms. Surgical resection followed by radiation and/or chemotherapy is widely accepted modality of treatment for high-grade gliomas. Magnetic resonance imaging (MRI) is fundamental to diagnose and characterize brain tumors, guide the surgical strategy and monitor treatment response. Diffusion-weighted Imaging (DWI) MRI has provided new advances and an improved understanding of the brain tumors. DWI provides a measure of tumor cellularity based on the restriction of the free diffusion of water in proliferating tissue. The tumor cellularity, as estimated through diffusion restriction, has been correlated with the degree of tumor malignancy. Raab et al. demonstrated differences for mean kurtosis (MK) and ADC values in WHO grade II-IV astrocytomas, with statistically significant higher MK values for high-grade gliomas (HGGs).[4]

In light of the 2016 update of the WHO brain tumor classification that stipulates an integrated layered diagnosis based on histological and molecular features, isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) mutations play a key role in the classification of gliomas.[9] According to the new biomarker-driven WHO classification, a proportion of these tumours, in particular those without IDH mutation and 1p/19q co-deletion, probably have represented IDH wild-type glioblastomas.

Elkhaled at al. found a significantly negative relationship between IDH-mutation status, as identified via 2-HG (2-hydroxyglutatarate) levels in tissue, and the rather lump apparent diffusion coefficient -ADC).[10] Xiong et al. demonstrated significantly lower minimum ADC in IDH wild-type oligodendrogliomas than in IDH-mutant by using DTI[11]. Findings of our study also show significantly lower ADC/NADC value representing significant diffusion restriction in IDH wild type tumors. Both the absolute mean ADC values and NADC appear valuable for this lesion type. However, ROI placement technique to calculate ADC can be subjective and prone to inter-observer differences.

Apart from the DWI studies, Patel et al. made an important contribution by introducing the 'T2-FLAIR mismatch' sign as a highly specific morphological feature of the IDH-mutant, 1p/19q non-co-deleted molecular subtype of astrocytomas.[12] This interesting finding was pronounced in this study as well. We found high signal intensity in T2WI and FLAIR sequences in IDH mutant tumors with facilitated diffusion representing low cellularity. Past studies to distinguish astrocytoma and oligodendroglioma using ADC values yielded variable success and in retrospect may have been influenced by the incomplete overlap between histological and molecular groups.[13,14] Diagnostic focus has shifted to genetic typing, yet immunohistochemistry tests are complex and not infallible, requiring interpretation in the context of morphological criteria and test type performed to avoid interpretational errors.[15]

In summary, the results from this study suggest that for newly diagnosed gliomas with lower ADC ratio values and less than 1 NADC value, further investigation with consideration of early tissue diagnosis is advisable given an increased risk of IDH^{wt} molecular status.

Conclusions

ADC measurement appears to be a simple and powerful method for molecular subtyping of high grade gliomas, specifically to identify IDH^{wt} neoplasms. Lower ADC ratio values and less than 1 NADC value warrants further investigation to rule out increased risk of IDH^{wt} molecular status. Large volume prospective study is

recommended for further evalutaion.

Conflict of Interest: None
Source(s) of support: None

Abbreviations

ADC	Apparent Diffusion Coefficient
MRI	Magnetic Resonance Imaging
IDH	Isocitrate Dehydrogenase
FLAIR	Fluid Attenuated Inversion Recover
DWI	Diffusion Weighted Imaging
CNS	Central Nervous system
EGFR	Endothelial Derived Growth Factor Receptor
CS	Centrum Semiovale
NADC	Normalized Apparent Diffusion Coefficient
WHO	World Health Organization
DTI	Diffusion Tensor imaging
ROI	Region of Interest

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