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Original Article

Can Apparent Diffusion Coefficient Predict the Grade, Genotype, or Proliferation Index of Oligodendrogliomas

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Abstract

Background: Genetic subsets of oligodendrogliomas (OD) have distinct chromosomal and biophysical profiles. Pretherapeutic tumor grade and genotype analysis is a challenging aspect of management, with 1p/19q codeletion status and grade of oligodendroglioma among the most important considerations for clinical decision making. **Methodology:** Seventy-three patients with histopathological diagnosis of oligodendroglioma were selected, and their preoperative 1.5T magnetic resonance imaging (MRI) scans were reviewed through parameters including diffusion weighted image, susceptibility-weighted imaging, and apparent diffusion coefficient (ADC). These images were correlated with patients' histopathological and chromosomal testing. Tumor border irregularity, homogeneity, contrast enhancement, and other MRI characteristics were also studied. For analysis, descriptive statistics were generated, and normality was evaluated for ADC value, age, and Ki-67 tumor proliferation index. **Objectives:** The study aimed to determine the correlation of ADC with Ki-67, grade, and 1p/19q co-deletion in oligodendroglioma at a tertiary care hospital within a low-middle income country. **Results:** Ki-67 tumor proliferation index was high in 33 tumors. It was found to be statistically significant ($P = 0.048$) with respect to ADC, showing that 1p/19q co-deleted tumors have a difference in their Ki-67 index. Ki-67 also showed a significant relationship ($P < 0.05$) with grade of OD. However, there was no statistically significant relationship between 1p19q chromosomal co-deletion and ADC. Linear regression was carried out as the data set was continuous. Univariate analysis showed no significant result with all P values above 0.10. **Conclusion:** Mean ADC is a viable tool to predict Ki-67 and assist prognostic clinical decisions. However, mean ADC alone cannot predict 1p/19q codeletion and tumor grades in OD. Further supplementation with other radiological modalities may provide greater yield and positive results.

Keywords: *Apparent diffusion coefficient, glioblastoma, magnetic resonance imaging*

Introduction

Gliomas are tumors of the white matter that are diffusely infiltrative and constitute approximately 80% of all brain tumors.[1,2] Oligodendrogliomas (OD) are a subtype of gliomas (according to the World Health Organization [WHO] 2016 classification of brain tumors), that are associated with a better prognosis, especially if associated with chromosome 1p/19q co-deletion.[3-7] The prevalence of this mutation is similar in both anaplastic (WHO grade 3) and low-grade OD[8] and the presence of this co-deletion is an independent predictor of remarkably better progression-free survival and overall survival.[9] The gold standard for diagnosis of OD and 1p/19q deletion status remains a biopsy for histopathology and gene analysis. However, more recently, several radiological features on magnetic resonance imaging (MRI) scans have been reported that are suggestive of diagnosis of OD and the co-deletion status.[4,10] This radiological differentiation is important for several reasons; it provides the treating physician a high index of suspicion prior to a formal biopsy, as despite significant advances in intraoperative aids and operative techniques, around 5% of biopsies yield tissue specimen that is insufficient in size or quality to demonstrate 1p/19q loss.[10] It may assist in the choice of tissue for sampling in case of difficult-to-access tumors. It may allow us a better understanding of the morphological differences between various types of OD, allowing a more elaborate classification system. Finally, in low-middle income countries, where genetic analysis is not

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widely available (there is only one center in our country of more than 200 million that performs genetic analysis on brain tumor specimen), an MRI scan may be the only aid to histopathology for subclassifying these tumors.

This, however, may only be possible if we can establish reliable radiological features that can predict the 1p/19q status of the OD, with high sensitivity and specificity. Megyesi *et al*. studied 33 patients and concluded that 1p/19q co-deletion OD stratification based on grading is possible through MRI alone.[11] This reflected that 1p/19q co-deleted tumors have distinct radiological features and this finding was further validated by Preusser *et al*. in their study of 67 patients with histological and molecular diagnosis of gliomas.[12] Apparent diffusion coefficient (ADC) was found to be the best differentiating characteristic between the different genetic subtypes of gliomas as also outlined in the 2016 WHO guidelines.[6,7] ADC is a measure of the magnitude of diffusion of water molecules found within the tissue. Values of ADC are automatically calculated, using a diffusion-weighted image (DWI), by software and displayed in the form of a parametric map highlighting the degree of diffusion of molecules of water through different types of tissues. Regions of Interest (ROIs) are used to define the region for which ADC values are being calculated. In addition, new modalities such as diffusion tensor magnetic resonance-derived metrics and arterial spin labeling are rapidly increasing the options available for precise, non-invasive testing based on radiological parameters.[13-17]

Based on these studies, we hypothesize that OD with 1p/19q chromosomal deletion is radiologically distinct from OD without 1p/19q loss. In this study, we attempted to explore whether 1p/19q codeletion, Ki-67, and tumor grade in OD can be reliably predicted based on mean ADC volumes on MRI scans in conjunction with other radiological features.

Methodology

Since the study was retrospective in nature, hospital records were reviewed and patients with biopsy-proven ODs were selected. The cohort was further narrowed by isolating patients with pre-surgery MRI scan, done using the in-house 1.5 Tesla scanner, and a biopsy specimen confirming the diagnosis of OD. The selected patients were then divided into those with 1p19q co-deletion and those without 1p19q co-deletion. The World Health Organization 2016 central nervous system tumor grading criteria were used to determine the grade of tumors.

Apart from ADC and grade, six additional parameters were investigated. Homogeneity within the tumors, regularity of tumor edge, necrosis, hemorrhage, calcification, and contrast enhancement were also reviewed in the MRIs. These were used to identify aggressive features in high-grade gliomas, aggressive features were classified as extensive necrosis, indeterminate edges, presence of hemorrhage, calcification, and strong contrast enhancement. Tumor location was decided to be set as the region or lobe containing the bulk (more than 80% of mass) of tumor. The corpus callosum was set as the point to distinguish unilateral and bilateral tumors, with OD traversing the corpus callosum considered to be bilateral. Allelic loss of chromosome was determined through loss of heterozygosity assays in tumor DNA pair. Microsatellite markers were used on chromosomes 1p36 and 19q13.

MRI imaging was done using a 1.5 Tesla (T) clinical MR imaging system (General Electric Signa HD MRI systems) using an eight-channel phased-array breast coil. A sample of these images is shown in Figures 1 and 2. A T2-weighted transverse pulse sequence was performed with 60/5600/180 (echo time/repetition time/inversion time) ms, 4 mm thickness, a field of view of 36 cm × 36 cm, and a matrix of 316 × 320. An axial plane was used to acquire DWI images and ADC maps were automatically created by the system using the trace-weighted images with b values of 0 and 1000. ADC values were calculated using the following formula: ADC = -(1/b) ln (S2/S1), where S2 and S1 are the intensity of signals at a b value of 1000 and 0, respectively. A sample of the imaging and some data generated are present in Figures 1 and 2.

The study underwent ethical review by the Aga Khan University Hospital Ethical Review Committee before data collection and analysis was done. No human interventions were involved throughout the study; no financial compensations were made to study participants. Data were stored in a secure password-protected folder on an encrypted computer accessible by the primary investigator.

Data analysis was divided into the three steps. First, we generated descriptive statistics (mean and standard deviation for continuous variables and frequency and proportions for categorical variables). Second, we evaluated normality for variables such as ADC value, Age, and Ki-67 tumor proliferation index (Histogram, Smirnov test of hypothesis for normality). Lastly, since the data were not normally distributed, we applied nonparametric tests to assess the relationship between predictors of ADC inferential statistics with a P value of alpha <0.05 set as a level of significance.

For our primary objectives, ADC was correlated with 1p19q codeletion, grade of tumor, and Ki-67 value. For our secondary objectives, MRI features were also correlated with tumor grade and 1p19q co-deletion separately. Details of each step are discussed in the results section below.

Results

Demographic and clinical characteristics of participants

A total of 73 patients participated in this study. The mean age of the patients was 38.86 years. The average value of ADC was found to be 1286.0. The study revealed that

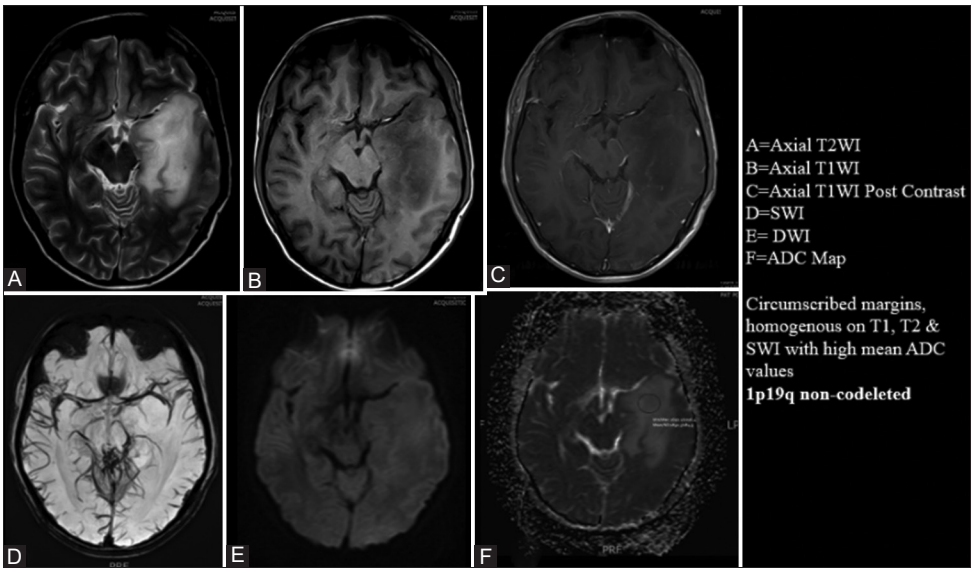

Figure 1: Sample of magnetic resonance imaging in a patient without 1p/19q codeletion

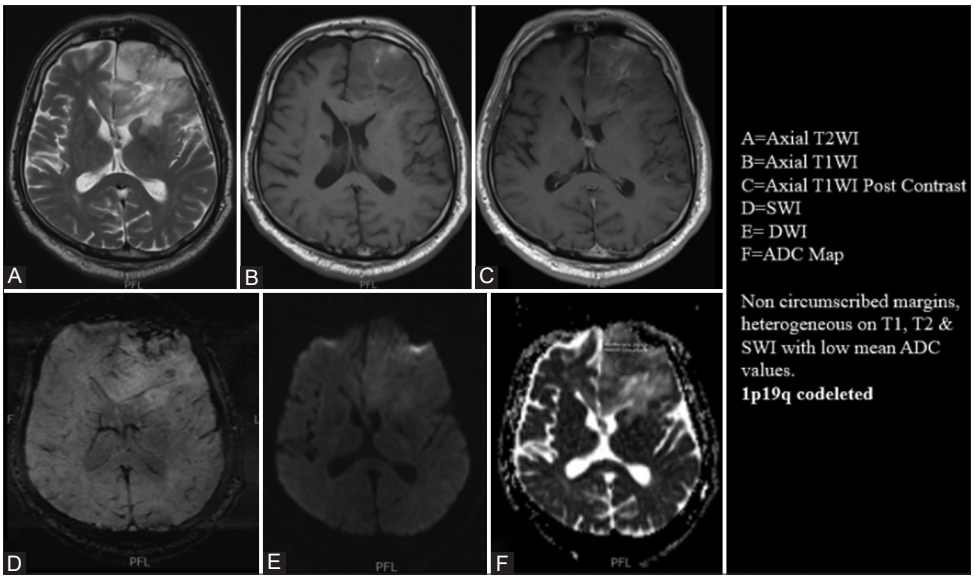

Figure 2: Sample of magnetic resonance imaging in a patient with 1p/19q codeletion

the majority of 49 (67.1%) patients were male; whereas, 24 (32.9%) were female. On histopathology, 39 (53.4%) were Grade II and 34 (46.6%) OD were grade III. Around 34 (46.6%) were co-deleted tumors and 39 (53.4%) were non co-deleted tumors in 1p19q genetic testing. [summarized in Table 1]

Forty-three (59%) tumors were located predominantly in the frontal lobe, 20 (27.3%) in the temporal lobe and 10 (13.7%) in the parietal lobe. Among Grade III OD, 2 (6.9%) showed no contrast enhancement, 23 (79.3%) showed some contrast enhancement and 4 (13.8%) showed homogenous contrast enhancement. Eighteen Grade II OD (72%) had shown no contrast enhancement, 6 (24%) showed some contrast enhancement, and 1 (4%) showed homogenous contrast enhancement.

Forty (54.8%) of the tumors had irregular margins, with 4 (5.5%) having smooth margins and 29 (39.7%) having indeterminate margins. Thirty-three (45.2%) of the tumors had cystic or necrotic changes visible while 40 (54.8%) did not.

Ki 67, an alternative assay of cellular proliferation, was identified for all 73 tumors and was found to be high in 33 (45.2%) tumors, low index in 25 (34.2%) and it was not available for 15 (20.5%) samples.

Sixty-five (89%) of the tumors were unilateral and 8 (11%) were bilateral. Forty-three (58.9%) tumors were located predominantly in the frontal lobe, 20 (27.4%) in the temporal lobe, and 10 (13.7%) in the parietal lobe as shown in Table 1.

Inferential statistics

We determined the predictors of ADC among patients with oligodendroglioma. The normality test showed that the data are not normal as shown in Table 2; therefore, we applied non-parametric tests.

In order to assess the relationship between predictors of ADC, inferential statistics such as Mann –Whitney test, Kruskal Wallis, and Spearman rank Correlation tests were run to analyze the dataset as shown in Table 3. *P* value of alpha less than 0.05 was set as level of significance.

Table 4 shows that only one variable, Ki-67 tumor proliferation index, was statistically associated with ADC level among patients with oligodendroglioma. Since *P* value (0.048) was <0.05 for Ki-67 tumor proliferation index and ADC. We conclude that there is a significant relationship between these two variables.

Linear regression analysis

Since the outcome variables were continuous in nature, linear regression analysis was carried out for the inferential statistics. Beta coefficient and their confidence intervals were computed as mean estimated change in ADC with one-unit change in the predictor variable.

Univariate analysis

Univariate analysis was run to analyze the independent effect of each independent variable with ADC. Each individual variable was individually regressed against ADC level. The results are shown in Table 5.

Discussion

Our results highlight that ADC is a good indicator of Ki-67. However, ADC alone is a weak indicator of 1p/19q co-deletion and tumor grade. Limitations based on population characteristics, sample size, and using one radiological parameter may be a possible reason for our results.

1p/19q co-deletion and apparent diffusion coefficient

The mean value of ADC of 1p/19q co-deleted tumors was not statistically significant (as *P* value was >0.05) from the mean ADC of non-co-deleted tumors in our study. This reflects literature which shows increased cellularity in 1p/19q co-deleted tumors in some cases but no significant difference in mean value of ADC alone.[10,18-21] This finding corresponds with Fellah *et al*. who reported a similar finding in 270 patients in their study on a single-center experience.[22] However, Jenkinson *et al*. report that tumors with 1p/19q loss are more likely to have a smaller mean ADC compared with tumors that do not have 1p/19q

Table 1: Descriptive Statistics of ADC among patients with Oligodendroglioma

Characteristics	Frequency (%)
Age*	38.86 (13.16)
ADC*	1286.0 (474.53)
Gender	
Male	49 (67.1)
Female	24 (32.9)
Grade of tumor	
II	39 (53.4)
III	34 (46.6)
1p/19q	
Co-deleted	34 (46.6)
non-co-deleted	39 (53.4)
Ki-67 tumor proliferation index	
Unavailable	15 (20.5)
Low	25 (34.2)
High	33 (45.2)
Affected side	
Uni-lobar	65 (89.0)
Bi-lobar	8 (11.0)
Site of Lobe	
Frontal	43 (58.9)
Temporal	20 (27.4)
Parietal	10 (13.7)

Table 2: Kolmogorov-Smirnov test statistics for normality testing

Variables	Test Statistics	*P*
Age	0.107	0.038
ADC	0.173	<0.001

Table 3: Inferential Test statistics according to types of variables

Association of Variables	Non-parametric Tests
ADC value * Age	Spearman Rank Correlation Coefficient
ADC value * Gender	Mann Whitney Test
ADC value * Histopathological Grade of tumors	Mann Whitney Test
ADC value * Ki-67 tumor proliferation index	Kruskal Wallis Test
ADC value * affected side	Mann Whitney Test
ADC value * site of lobe	Kruskal Wallis Test
ADC value * 1p19q co-deleted tumors and non -co deleted tumors	Mann Whitney Test

Table 4: Inferential Statistics of ADC among patients with Oligodendroglioma

Characteristics	Test statistics	*P*
Age*	-0.171	0.147
Gender	569.0	0.823
Grade of tumor	564.5	0.276
Type of tumor (1p/19q)	522.5	0.12
Ki-67 tumor proliferation index	6.061	0.048
Affected side	209.50	0.372
Site of Lobe	1.323	0.516

Table 5: Univariate Analysis of Determinants

Characteristics	B (SE [β])	*P*	95% CI
Age	-3.064 (4.261)	0.474	(-11560, 5.432)
Gender	-16.326 (119.045)	0.891	(-253.694, 221.042)
Grade of tumor	-23.563 (112.089)	0.834	(-247.062, 199.937)
Type of tumor (1p/19q)	-138.293 (110.916)	0.217	(-359.454, 82.868)
Ki-67 tumor proliferation index	-106.057 (71.301)	0.141	(-248.226, 36.113)
Affected side	51.100 (178.945)	0.776	(-305.706, 407.906)
Site of lobe	92.379 (76.657)	0.232	(-60.470, 245.229)

chromosomal deletion.[23] In our results, we see a trend similar to that found by Fellah *et al*. which concluded that mean ADC alone is not sufficient as a modality to distinguish between 1p/19q co-deleted and non-co-deleted tumors. Other modalities such as cerebral blood volume might serve as an adjunct parameter to introduce significance for a radiological testing modality.[22] Moreover, Abdel Razzak *et al*. have demonstrated the advent of new modalities such as arterial spin imaging, diffusion tensor imaging, and their respectively derived metrics as viable alternatives to conventional DWI based metrics.[14,15,17]

Ki-67 and apparent diffusion coefficient

In a study by Preusser *et al*. in 2012, Ki-67 was evaluated as a clinical and prognostic tool and was found to have a strong prognostic impact.[12] In our study, the OD with the lowest Ki-67 index were all non 1p/19q co-deleted tumors, while the 1p/19q co-deleted tumors had a higher ratio of tumors with a high Ki-67 index. Ki-67 values were also significantly different (with $P = 0.048$) between different tumor grades making Ki-67 a viable predictor for tumor grades. Studies by Pouget *et al*. and Duregon *et al*. both investigate the prognostic impact of Ki-67 in OD with 1p/19q codeletion and both conclude that Ki-67 is a strong predictor of prognosis.[24,25] This conclusion correlates with other literature, pointing towards the idea that Ki-67 could be used to support prognostic and therapeutic clinical decisions.[26,27]

Tumor grade and apparent diffusion coefficient

Mean ADC for grade III OD, irrespective of 1p/19q co-deletion, was 1273, while mean ADC for grade II OD was 1300. A lower mean ADC is a marker of higher cellularity that corresponds with the histological grade of the tumors. Latysheva *et al*. reported in 2019 that Histogram derived ADC parameters could successfully distinguish between OD and oligoastrocytoma.[28] Similarly, Anwar *et al*. report a significant difference in ADC mapping for different tumors.[29] However, data in our study does not demonstrate a significant ($P < 0.05$) difference between mean ADC of OD Grade II and III. These findings are reflected in literature by Hilario *et al*. and Fellah *et al*. who also found no significant correlation between grade of OD and the mean value of ADC.[18,22] Naveed *et al*. who further explored grading of OD through MRI concluded that ADC values when combined with relative cerebral blood volume and MR spectroscopy is sufficient in differentiating groups of OD.[30] Thus, a study combining mean ADC with other radiological parameters[19,31] such as MR spectroscopy[32] or rCBV may yield a significant result in distinguishing grades of OD based purely on radiological characteristics.

Other radiological characteristics and 1p/19q co-deletion

Co-deletion of 1p19q in OD is likely due to recurring translocation and may be a marker of therapeutic response to chemotherapy and overall long-term survival. Some basis for radiological distinction between OD based on 1p/19q loss has already been reported in literature. Megyesi *et al*. showed that OD with 1p/19q loss showed indistinct borders, paramagnetic susceptibility, and calcification more commonly than their counterparts.[11] In our data, almost half (54.7%) of the tumors had irregular borders, while 39.4% had indeterminate borders. None of the tumors with 1p/19q co-deletion were found to have smooth borders, the majority having indeterminate borders. Homogenous signal intensity was also found more commonly in tumors with higher ADC, and tumors with noncircumscribed borders were found only above a mean ADC of 1000 mm^2/s.

A study published as far back as 2001 showed that bi-hemispherical growth patterns and peripheral tumor location had a significant correlation with chromosomal 1p/19q codeletion.[33] Our data showed that 59% of our subjects had the tumor present in the frontal lobe, with the second most common site being the temporal lobe. 1p/19q co-deleted OD had twenty-three (67.6%) tumors present in the frontal lobe, seven (20.6%) in the parietal lobe and four (11.8%) in the temporal lobe. In contrast, 1p/19q non-co-deleted OD had 18 (50%) tumors in the frontal lobe, 12 (33.3%) in the parietal lobe, and six (16.7%) tumors in the temporal lobe.

Other radiological characteristics and grade of tumor

Grade III tumors in our study showed significant partial or homogenous contrast enhancement when compared with Grade II OD. Similarly, Grade III tumors showed a greater ratio of indeterminate edges, necrosis, and cystic changes. In Grade III OD, 1p/19q codeletion has been associated with distinct radiological characteristics,[20] particularly blurred tumor borders, frontal lobe location, and intra-tumoral signal heterogeneity.[34]

Quantitative analysis of MRI has demonstrated a high sensitivity and specificity to 1p/19q chromosomal codeletion.[10] Another research has shown that angiogenic

subtypes of OD that are distinguishable on MRI can also be indicative of 1p/19q loss and other chromosomal deletions.[35] This research is aided by the fact that sufficient advances in MRI techniques and analytical tools have also allowed for more introspective analysis and quantitative logging of features extracted from images of tumors.[17,21]

Currently, diagnostic testing of OD tumors for chromosomal deletions such as 1p/19q is not widely available even in more developed regions. In a low-resource and population intensive region, there are very limited centers where chromosomal testing is available, and even where available the cost is prohibitive. The technical expertise required to analyze and correctly interpret the data are often lacking. Fluorescence *in situ* hybridization and loss of heterozygosity studies present an appealing alternative but hold their own drawbacks. Inherent sampling errors and difficulty in residual tumor evaluation are two major ones.

An alternative method of predicting molecular and pathological patterns in OD is emerging with the evolution of radiological techniques. MRI studies, which are done for the diagnosis of all ODs, can serve as an analytical tool based on software analysis and mapping techniques. This would further aid clinical and surgical decision-making in providing a patient-oriented approach with each case.

Conclusion

We conclude that mean ADC is a useful diagnostic tool in predicting Ki-67 values of OD and thus overall prognosis. However, mean ADC alone would not improve prebiopsy discrimination of 1p/19q co-deleted tumors from 1p/19q nonco-deleted tumors at the moment. Histopathological examination remains the gold standard for classification and grading of brain tumors. Even though radiological features may be suggestive of certain grades and genotypes, with the technology currently available in developing countries, it continues to show low sensitivity and specificity.

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Conflicts of interest

There are no conflicts of interest.

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