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Total magnitude of diffusion tensor imaging as an effective tool for the differentiation of glioma

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ABSTRACT

Objectives: The study aims to evaluate the difference in diffusion properties between high grade glioma and low grade glioma by measuring the total magnitude of diffusion tensor (L), and its isotropic (p) and anisotropic (q) components.
Methods: The diffusion tensor parameters p, q, L and FA from the tumor area, adjacent area to the tumor and corresponding contra lateral normal area of 30 high grade glioma and 49 low grade glioma were calculated. Chi square analysis was done to find the changes in age and sex. One Way ANOVA was performed to compare the mean and ROC curve analysis to confirm the discriminative sensitivity.
Results: Major variation in the mean values of p, L and FA was observed in different brain areas considered. Variation in the p and L values between low grade and high grade glioma were statistically significant ($p < 0.001$) and their ROC curve analysis yielded 93.9% and 91.8% sensitivity and 53.3% specificity respectively.
Conclusion: Measurement of the isotropic component p and the total value of diffusion tensor L can be effectively correlated with different grades of glioma and can be used to study the diffusion properties of tumor affected brain.

1. Introduction

Gliomas arise from the neuroepithelial tissue with main morphologic subtype being the astrocytomas which represents 75% of gliomas, oligodendrogliomas with 8.4% and fast growing highly infiltrating glioblastoma multiforme which account for 18.5% of all primary brain tumors [1]. Glioma tissues are heterogeneous in nature, and during malignant transformation the histopathologic features of the tumor change substantially, reflecting alterations in tumor microvasculature. Infiltrating gliomas mainly invade along white matter tracts. Due to this diffuse infiltration, gliomas have a poor prognosis. The detection, choice of biopsy site and reliable quantification of white matter tumor infiltration are very important for the determination of optimum treatment strategy [2] and thus makes the analysis a challenging issue.

DTI is the only non-invasive method that is capable of quantitative analysis of the white matter. Its application has already been exploited to identify different tumor components, to differentiate tumor invasion from normal brain tissue or edema, subtype low grade gliomas and differentiate cerebral lymphoma from glioblastoma [3–8].

Quantitative DTI has gained major importance due to the application in the diagnosis and prognosis of brain diseases. Pena et al. [9] reported the mathematical technique to enhance the visualization and quantification of brain tissue using DTI. The introduction of parameters like pure isotropic diffusion (p), pure anisotropic diffusion (q) and total magnitude of diffusion tensor (L) derived from eigen values can quantify DTI [9–12]. There are only few studies [9–13], which explains the biological characteristics of glioma using p, q and L parameters of DTI. Moreover, a differentiation between different grades of tumor is also lacking among these studies. We, in this report hypothesize that p, q and L metrics of DTI can be used to differentiate high grade and low grade gliomas. These metrics can also be used to identify different areas in the tumor affected brain.

Abbreviations: ROC, receiver operating characteristic analysis; FA, fractional anisotropy; MD, mean diffusivity; TR, time of repetition; TE, time of echo; FOV, field of view; NEX, number of excitation; ROI, region of interest; AUC, area under the curve.

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Table 1
Mean and standard deviation from One Way ANOVA analysis of DTI metrics for low and high grade glioma.

	Low grade glioma	High grade glioma	Significance (p)
p value ($\times 10^{-3}$ mm^2 s^{-1})	3.446 ± 0.902	2.562 ± 0.774	0.001
q value ($\times 10^{-3}$ mm^2 s^{-1})	0.406 ± 0.12	0.359 ± 0.099	0.05
L value ($\times 10^{-3}$ mm^2 s^{-1})	3.471 ± 0.903	2.590 ± 0.769	0.001
FA	0.147 ± 0.043	0.181 ± 0.065	0.003

2. Materials and methods

The study was performed prospectively on 79 glioma patients, with a mean age of 40 years ranging from 18 to 68 years. This included 30 high grade glioma (11 glioblastoma, 13 grade III astrocytoma and 6 grade III oligoastrocytoma) and 49 low grade glioma (22 grade I astrocytoma, 5 grade II astrocytoma, 17 grade I oligoastrocytoma and 5 grade II oligoastrocytoma) as per histopathological evaluation. The study was approved by the Ethics Committee of Sree Chitra Tirunal Institute for Medical Sciences and Technology. Informed consent was obtained from all the patients who participated in the study. The imaging of all patients was done before surgery on a 1.5 Tesla MR system (Avanto TIM; Siemens, Erlangen, Germany) using a 12-channel phased array head coil. Each patient underwent conventional MRI with *T*1, *T*2, FLAIR and post contrast *T*1 sequences. The DTI imaging protocol used a Spin-Echo Echo planar DTI sequence with diffusion gradients along 30 non collinear directions with the imaging parameters of TR = 3500 ms, TE = 105 ms, Image matrix = 192 × 192, FOV = 230 × 230 mm, slice thickness = 5 mm with distance factor of 1.5 mm, NEX = 1 and b factor 0 and 1000 s/mm^2. Diffusion tensor images were processed and reconstructed in a separate work station (Leonardo workstation; Siemens Medical systems). All regions of interest were inspected, identified and approved by a well-qualified Neuroradiologist (A K G). Post contrast *T*1 weighted images as well as eigen value images were loaded to the processing workstation. Post contrast *T*1 weighted images were used for selecting the regions of interest as the tumor area could be clearly seen on these images. Circular regions of interest of 1–5 mm^2 were placed in the axial post contrast images. These ROIs simultaneously gets displayed on the eigen maps from which the eigen values λ_1, λ_2, λ_3 were extracted from different voxels of the tumor region. Areas of hemorrhage, necrosis and nonbrain regions like CSF and ventricles were excluded from the analysis. Measurements were repeated on 5 to 6 adjacent slices from the starting to the end of the tumor i.e. the eigen values are measured from a 3D tumor volume. The same procedure was repeated to get the eigen values from other non tumoral areas. The p, q, L, and FA values were calculated using the following equations.

$$\mathrm{ADC} = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} \quad (1)$$

$$p = \frac{\lambda_1 + \lambda_2 + \lambda_3}{\sqrt{3}} \quad (2)$$

$$q = \sqrt{[(\lambda_1 - D)^2 + (\lambda_2 - D)^2 + (\lambda_3 - D)^2]} \quad (3)$$

$$L = \sqrt{(p^2 + q^2)} \quad (4)$$

$$\mathrm{FA} = \sqrt{\frac{3}{2}} \times \frac{q}{L} \quad (5)$$

2.1. Statistical analysis

Chi square analysis was used to find the difference in patient age and sex between the groups. ANOVA test was performed on patient groups with high grade glioma and low grade glioma to evaluate the variations in the p, q, L and FA values, using the Statistical Package for Social Sciences, SPSS PC version 17.0 for Windows (SPSS 17, SPSS Inc., Chicago, IL, USA) (Table 1). The level of significance was considered to be less than 0.05. The ROC curve analyses were done with the same software. The ROC curve was used for calculating the area under the curve (AUC), an index of overall discriminative ability of a given method. The AUC of each ROC was considered good if >0.60.

3. Results

Chi Square analysis for difference between patient age was not significant (low grade versus high grade glioma: mean, 36.3 versus 45.7, $p = 0.848$) and the test for differences in sex was also insignificant ($p = 0.144$). Examples of post contrast images and eigen value maps of high grade and low grade glioma used in this study are shown in Fig. 1. The values of p, q, L and FA of all the ROI's from tumor, adjacent area to the tumor and contra lateral area of low and high grade glioma are given as boxplots in Fig. 2(a–d), respectively. Results of the One Way ANOVA analysis between two different tumor types are shown in Table 1. ROC curve analysis of p, q, L and FA values between high grade and low grade glioma are given in Table 2. In all cases, p and L values of the tumor regions are found to be significantly high compared to the non tumoral regions considered. But interestingly, high grade gliomas showed the lowest range of p and L values compared to low grade glioma. Significant reduction in the FA value was also observed in all the tumor sites of high grade glioma compared to adjacent area to the tumor and corresponding contra lateral normal area. The p value in the high grade glioma ranged from 0.992×10^{-3} to 3.879×10^{-3} mm^2 s^{-1}, with an average value of $2.562 \pm 0.0774 \times 10^{-3}$ mm^2 s^{-1} (mean ± SD). The L value in the high grade glioma ranged from 1.003×10^{-3} to 3.911×10^{-3} mm^2 s^{-1}, with an average value of $2.590 \pm 0.769 \times 10^{-3}$ mm^2 s^{-1} (mean ± SD). In high grade glioma, the range of FA values was found to be between 0.062 and 0.415 with the mean value and standard deviation, 0.181 ± 0.065.

Low grade glioma has the highest mean p and L value among all the tumors evaluated. The p value in low grade glioma ranged from 2.041×10^{-3} to 4.937×10^{-3} mm^2 s^{-1} with an average value of $3.446 \pm 0.902 \times 10^{-3}$ mm^2 s^{-1} (mean ± SD). The L value has a range of 2.062×10^{-3} to 4.979×10^{-3} mm^2 s^{-1}, with an average value $3.471 \pm 0.903 \times 10^{-3}$ mm^2 s^{-1} (mean ± SD) in low grade glioma. The FA value in the low grade glioma extended from 0.094 to 0.289 with a mean and standard deviation, 0.147 ± 0.043. The mean FA value in low grade glioma is significantly lower than that of high grade glioma ($p < 0.003$).

The q value of high grade gliomas is significantly lower than that of low grade glioma ($p < 0.05$). We have not observed any significant difference in the q value between the tumor affected area and normal brain area (Fig. 2b). Sensitivity, specificity, AUC and significance yielded by the ROC curve analysis of high and low grade glioma performed for the parameters p, q, L, and FA are given in Table 2.

4. Discussion

There are few promising works based on DTI metrics p and q regarding the tissue characterization of diffusion tensor