Multi-Compartment Diffusion Analysis for Differentiation of Malignant and Benign Brain Tumors in Pediatric Patients

Jie Deng[1,2], Delilah Burrowes[1], and Emma Boylan[1]

[1]*Medical Imaging, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, United States,* [2]*Radiology, Feinberg School of Medicine, Northwestern University, Chicago, IL, United States*

BACKGROUND

Diffusion weighted MRI (DW-MRI) was initially developed and primarily used to evaluate ischemic disease of the brain. It's application and utilization has been vastly increased over the past decade particularly with its utilization in assessing and characterizing brain tumors. Conventional DW-MRI acquires 2-3 diffusion-weighted images with b-values less than 1000 s/mm^2 to calculate the apparent diffusion coefficient (ADC). In theory, brain tumor lesions showing lower ADC (i.e. more restricted diffusion) indicate increased tissue density suggesting an increase in malignancy. However, there is a great overlap in ADC between tumor grades and types limiting ADC as a reliable diagnosis tool[1]. It has been reported that water molecular diffusion in brain tissue is anomalous at high b-values (e.g. >1500 s/mm^2) [2]. Several complex models have been developed to characterize diffusion behavior at higher b values (e.g. up to 4000 s/mm^2) to infer tissue microstructural properties and microenvironment [3-5]. An anomalous diffusion model expressed through fractional order calculus derives a complex parameter β (0<β<1) and a space constant μ (unit: μm). The β and μ were found to correlate with the porosity and tortuosity of a phantom gel structure and brain tissue; a decreased β represents an increase in tortuosity and heterogeneity and an increased μ reflects more restricted diffusion (i.e. less free movement of diffusion molecules). A bi-exponential two-compartment model assumes two main water populations: a low mobility water component representing intracellular/bound water molecules and a high mobility water component representing extracelluar/free water molecules. The purpose of this pilot study was to evaluate the anomalous diffusion model and bi-exponential two-compartment model in differentiation of malignant and benign tumors in pediatric patients.

METHODS

MRI Images were acquired on 1.5T and 3.0T MRI scanners (Magnetom Avanto/Aera/Skyra, Siemens Medical Solution). Diffusion weighted echo-planar imaging (DW-EPI) with 16 extended b-values (0-3500 s/mm^2) was acquired with the following parameters: FOV=230×190 mm^2, matrix = 144×112, TR = 4000 ms, TE = minimum, BW = 1021 Hz/px, averages = 3, number of slices = 15-25 to cover entire tumor areas.

Data Analysis A region of interest (ROI) was placed on each solid tumor area and averaged signal intenisty (S) at each b-value were measured within each tumor ROI. Conventional ADC value was calculated using a mono-exponential model fitting signal decay with b=0-1000 s/mm^2. Extended diffusion parameters were derived from two diffusion models, separately, using an in-house developed Matlab software.

Anomalous Diffusion Model: Signal intensities at 16 b-values (0-3500 s/mm^2) were fitted based on the equation: $S(b)/S_0 = \exp[-D\cdot\mu^{2(\beta-1)}\cdot(\gamma G_d\delta)^{2\beta}\cdot(\Delta-(2\beta-1)\cdot\delta/(2\beta+1))]$, where G_d is diffusion gradient amplitude, δ and Δ are diffusion gradient pulse width and separation interval, respectively. Anomalous diffusion parameters μ and β were derived by the Levenberg–Marquardt fitting.

Bi-exponential Two-Compartment Model: Signal intensities at 11 b-values from 150-3500 s/mm^2 were fitted based on the equation: $S(b)/S_0 = V_{fast}\cdot\exp(-D_{fast}\cdot b) + V_{slow}\cdot\exp(-D_{slow}\cdot b)$. Extracellular diffusion coefficient (D_{fast}) and volume (V_{fast}) and intracellular diffusion coefficient (D_{slow}) and volume (V_{slow}) were derived by the Levenberg–Marquardt fitting.

Statistical Analysis Each diffusion parameter (ADC, μ, β, D_{slow}, V_{slow}, D_{fast} and V_{fast}) was compared between malignant and benign tumor groups using non-pair t-test with unequal variance (α =0.05).

RESULTS

The study was performed on a total of 21 patients (2-18 years) with biopsy-proven brain tumors, divided into malignant and benign groups. Malignant tumor group (N=11) included high-grade glioma, anaplastic medullobladtoma, pineoblastoma, astroblastoma, alveolar rhabdomyosarcoma and grade II diffuse fibrillar astrocytoma. Benign tumor group (N=10) included low-grade glioma, pilomyxoid astrocytoma, pleomorphic xanoastrocytoma and juvenile polycystic astrocytoma.

Among all diffusion parameters, ADC, μ, β, V_{slow} all demonstrated significant differences between malignant and benign tumors with p-values (*p*) <0.005. D_{fast} also showed significant difference with $p = 0.01$, whereas D_{slow} did not differ between tumor types with $p = 0.4$. Noticeably, there was no overlap between the two groups when comparing their μ values (Fig. B); whereas ADC, β and V_{slow} values showed some degree of overlapping between tumor groups (Fig. A,C,D).

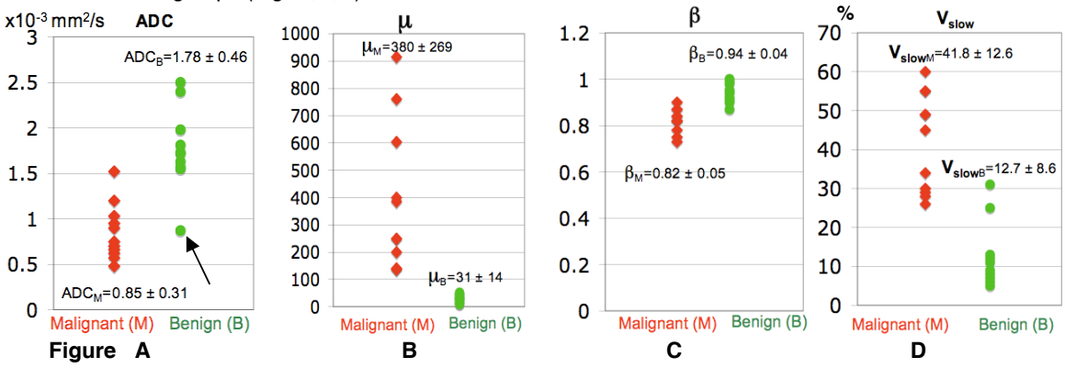

Figure A **B** **C** **D**

DISCUSSIONS

The findings in this study were consistent with the theoretical explanation of diffusion properties in brain tumor lesions. Malignant tumors are characterized with more compact tissue density, higher intracellular volume and increased tortuosity and heterogeneity. These tissue properties were reflected as lower ADC, lower β (i.e. increased complexity), higher intracellular volume V_{slow} and dramatically increased space constant μ, compared to benign tumors. The space constant μ was the most sensitive parameter that differentiated malignant and benign tumor by 100% in this study. In one patient with low-grade glioma, the tumor ADC value (arrow in Fig.A) was very low (=0.87 mm^2/s) that may potentially be misdiagnosed representing a higher-grade neoplasm; however, its low μ (=45), relatively high β (=0.92) and low V_{slow} (7%) characterized it as a benign tumor.

CONCLUSIONS

This study shows a strong correlation in differentiating malignant and benign brain tumor types using simultaneous evaluation of multiple diffusion parameters. This method may prove to be useful in improving the accuracy and confidence in the diagnosis of various brain tumors, facilitating treatment planning, targeting treated tumor areas and in therapeutic response assessment.

References: [1]. Kan P, et al. Childs Nerv Syst 2006; 22: 1435–39. [2]. Le Bihan D. et al. Phys Med Biol 2007;52:R57–R90. [3]. Magin R, et al. J Magn Reson 2008; 190: 255–270. [4]. Gao Q, et al. J Magn Res Imag 2011; 33:1177–1183. [5]. Mardor, Y, et al. J Clin Onc Vol21, No 6:1094-1100.