Imaging biomarkers in neurofibromatosis 2-related vestibular schwannomas

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Introduction

Neurofibramatosis type-2 is characterized by the presence of bilateral vestibular schwannomas (VS). These benign tumors cause progressive hearing loss and brainstem compression. Current treatment options, including surgery and radiotherapy, can result in hearing loss, facial weakness and dysphagia [1]. However, a recent paper showed that treatment with Bevacizumab, an anti-VEGF antibody, improves hearing and reduces tumor volume in the majority of progressive vestibular schwannomas [2]. Furthermore, advanced imaging techniques (e.g., DCE-MRI, DSC-MRI and DTI) can be used to assess tumor biology and function non-invasively, particularly in the context of anti-angiogenic therapy. To this end, we developed an automated method for identifying vascular input functions to improve estimates of Ktrans using DCE-MRI. We have also implemented a combined gradient- and spin-echo DSC-MRI sequence for estimates of relative cerebral blood volume (rCBV) acquired high resolution DTI data for estimates of tumor diffusion coefficients. Overall, these advanced imaging techniques provide a unique opportunity to identify predictors of clinical response based on tumor volume, functionality and other clinical indictors in a highly heterogeneous tumor type.

Methods

NF2 patients with evidence of disease progression were eligible for participation in this trial. Progression was defined as growth based on serial MRI scans or hearing loss based on serial audiology. The progressive VS was defined as the "target" VSPatients were scanned on a 3 Tesla imaging spectrometer (TimTrio, Siemens Medical Solutions, Malvern, PA) 24 hour prior to initiation of treatment, then every 2 months following that initiation date. To derive estimations of permeability, a voxel-by-voxel T1 map was derived using a variable flip angle (2, 5, 10, 15, 30 degrees) fast volumetric GRE acquisition, followed by a dynamic series employing two echo times (TE=2.73, 3.89ms) acquired at a 6s time resolution and 2.6 x 1.8 x 2.1 voxel resolution. A 0.1 mmol/kg dose of GdDTPA was injected at a rate of 5 cc/s within 2.5 minutes of the start of the acquisition. The addition of a second echo in the dynamic GRE sequence allows for a potentially robust way to correct for T2* effects in voxels that contain high concentrations, as in the arterial and venous voxels. Perfusion imaging was performed using a combined gradient- and spin-echo EPI (TE=31, 96ms) acquired at 0.6s time resolution and a 1.2x1.2x2 voxel resolution. A 0.2 mmol/kg dose of GdDTPA was injected at 5cc/second after 78 seconds of imaging. EP diffusion-weighted images were acquired with TR 7500 ms, TE 84 ms and a b-value of 700 s/mm^2 in 90 directions as well as 7 low b value images (b ~ 0 s/mm^2) to allow reconstruction of the diffusion tensor at each voxel.

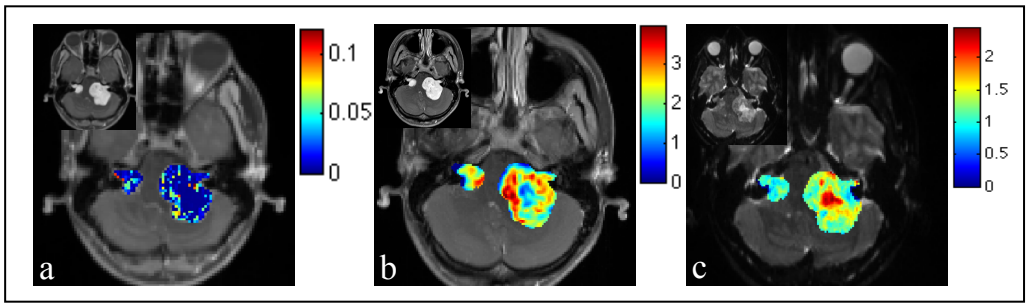

Figure 1. a) DCE-MRI derived K^{trans} map (min^{-1}); b) DSC-MRI derived rCBV map (unitless); c) ADC map (mm^2/s).

Results & Discussion

Figure 1 illustrates the regional variation K^{trans} (a), the relative cerebral blood volume (rCBV) (b) and the diffusion coefficient (c) in the target (left) and contralateral (right) VS from a representative patient. This internal heterogeneity was not apparent on routine scans acquired prior to the study. Table 1 lists mean parameter values for the target and contralateral VS for all tumors. Variations in K^{trans} within VS were observed across patients and between tumors (range, 0.021 – 0.121 min^{-1}) within the same patient. The parameter with the greatest difference between target and contralateral VS was the relative cerebral blood volume (rCBV), where the mean rCBV was nearly 2 fold higher in target VS (p=0.009). The diffusion coefficient was higher in the target VS than the contralateral VS, although this difference was not statistically significant. In the course of this study, we hope to identify a robust imaging biomarker to select patients with progressive VS who are likely to respond to anti-antiogenic therapy.

	K^{trans} (min^{-1})		rCBV		ADC (x 10^{-3} mm^2/s)	
	Target VS	Contra-VS	Target VS	Contra-VS	Target VS	Contra-VS
Patient 1	0.047	0.036	1.882	1.336	1.301	0.980
Patient 2	n/a	n/a	1.708	0.584	1.614	1.350
Patient 4	0.021	0.044	1.494	0.286	1.052	1.055
Patient 5	0.045	0.047	1.080	0.230	1.231	1.140
Patient 6	0.060	0.065	0.826	0.341	1.625	2.249
Patient 7	0.032	0.039	1.207	0.735	1.220	0.253
Patient 10	0.121	0.106	1.738	1.381	1.447	1.399
Mean	0.054	0.056	0.699	1.419	1.330	1.201
p-value	0.92		0.009		0.54	

References [1] Roswell, E., et al., Neurosurgery 30:962, 1992.

[2] Plotkin, S., et al., NEJM 361:358, 2009.