Novel DTI Studies of NF1 Gliomas in Mice and Children

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Introduction: Neurofibromatoses are a set of genetic disorders that can cause tumors to grow on all types of nerves, and can also affect the development of non-nervous tissue, such as bones and skin. Children with Neurofibromatosis Type 1 (NF1) who develop optic pathway glioma (OPG) face a potentially devastating loss of vision. Presently, there is no reliable way to distinguish OPG that will result in visual loss and require treatment from those that will follow a more benign clinical course. Furthermore, there are sparse quantitative data correlating MRI with underlying histology or with clinical outcome in OPG. The recent development of *GFAPCre; Nf1*$^{flox/mut}$ mice[1] that develop OPG that strongly parallel OPG in children with NF1 offers exciting new avenues for translational research. Here, we report the use of DTI to analyze OPG development and progression in both mice and children.

Methods: Imaging experiments on mice were performed on a small-animal MR scanner built around an Oxford 4.7 T magnet (33 cm clear bore) and high-performance gradients (15-cm inner diameter) and a Varian INOVA console. The imaging studies of children were performed on a 3.0 T Siemens Trio or a 1.5 T Siemens Sonata. Standard, 6-direction DTI data were acquired and diffusion parameters, including ADC, RA, and principal diffusivities measured.

Results: As illustrated in Figure 1 (left), optic nerves in mice can be identified as regions of high anisotropic diffusion (red ellipses) on RA maps derived from DTI data.[2] To probe for the presence of OPG, we perform DTI experiments to identify the position and size of the optic nerve, and then overlay the outlines of these optic nerves on standard T2-weighted images. Figure 1 (middle) shows such an image of a normal, control mouse, in which there is a void between the two optic nerves. By contrast, in the image of a transgenic mouse with OPG (Figure 1, right), a mass of tissue, highlighted by the yellow arrow, can be clearly seen between the optic nerves. The presence of OPG was confirmed histologically in this mouse. We have examined approximately 24 *GFAPCre; Nf1*$^{flox/mut}$ mice spanning 2 – 12 months in age. In all mice, we observed abnormal signal corresponding to optic nerve/chiasm tumors. For all cases when diffusion tensor imaging was abnormal, tumor was evident. Similarly, all pathologically verified tumors had MR correlates. As in the human studies described below, the ADC values of the optic nerve tumors in *GFAPCre; Nf1*$^{flox/mut}$ mice are greater than corresponding values in healthy brain tissue, with values in tumors ranging from 1.1 to 2.5-fold greater than healthy brain.

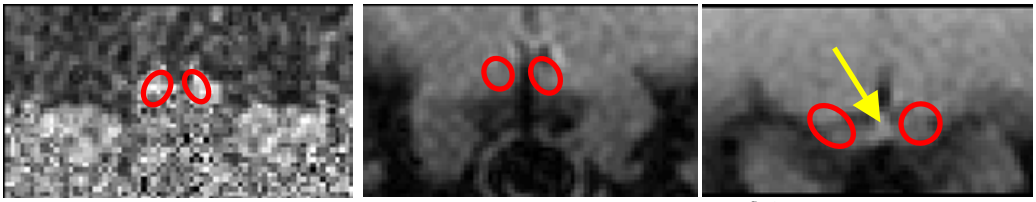

Figure 1. RA map(left), T2-weighted images of control (middle) and *GFAPCre; Nf1*$^{flox/mut}$ mice (right). Optic nerves are identified by red ellipses; the yellow arrow highlights OPG in the *Nf1*$^{flox/mut}$ mouse .

Initial human imaging experiments of OPG were performed at 1.5 T. Recently, we have transferred these experiments to a new 3 T system and have observed a significant increase in both signal-to-noise and image resolution. Representative 3 T images of a child with an NF1 OPG are shown in Figure 2. The black arrow indicates the OPG on sagittal (left) and coronal (middle) MPRAGE images. To date, we have characterized OPG in 10 NF1 patients using DTI methods. Based upon previous work[3], we expect stable NF1-associated OPG to have higher ADC and higher RA than the more aggressive NF1-associated and sporadic OPG. Nine of ten NF1 patients studied by MRI have stable tumors. For these patients, the ratio of the ADC measured for OPG relative to normal brain tissue is greater than 1, ranging in value from 1.24-1.53 (Average = 1.38; SD = 0.13). The ADC map for one of these patients is illustrated in Figure 2 (right). In a tenth NF1 patient, having an aggressive tumor, this ADC ratio is 0.93.

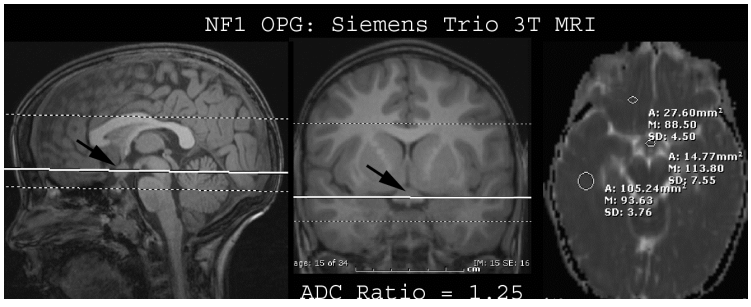

Figure 2. MPRAGE images (left, center) and ADC map (right) of OPG in an NF1 patient

While preliminary, these results suggest that ADC may be a useful MR biomarker for distinguishing stable and aggressive OPG in NF1 patients. Together with our foundational small-animal studies, we believe MR holds great promise for improving early detection, providing more accurate mapping of tumor burden, and for evaluating novel therapies for NF1-associated OPG.

References:

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