MRI characteristics of Primitive Neuroectodermal Tumors (PNETs) in a spontaneous JCV T-antigen transgenic mouse brain tumor model at 7 Tesla

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Background and Objective

Medulloblastomas also referred to as a primitive neuroectodermal tumors (PNETs) when arising from the cerebellum, are highly cellular malignant primary brain tumors in children (Rutka et al. 1997) (Zee et al. 1993) and adults (Malheiros et al. 2003). PNETs represent approximately 20% of intracranial neoplasms in children and 1% in adults. They originate from primitive neuroepithelial cells located in the cerebellar vermis. Patients typically present with a few week history of dizziness, morning headache, nausea, and weakness. On clinical presentation approximately 25% of PNETs demonstrate cerebral spinal fluid metastatic spread. Modern therapy is limited to a gross total resection of the tumor followed by irradiation of the complete spinal neuraxis. The current five-year survival rate is approximately 60%. Magnetic Resonance Imaging (MRI) is the primary diagnostic imaging tool for brain tumors in humans (Golfinos et al. 2004). However it lacks from its inability to clearly define the tumor normal parenchymal interface; to differentiate tumoral edema from infiltration; inability to diagnose small primary or metastatic lesions; and to differentiate PNETs from other primary CNS neoplasm. It is therefore necessary to study the imaging characteristics of these CNS tumors using animal models. The human neurotropic virus, JC virus, encodes an oncogenic regulatory protein, T-antigen, which has been detected in a broad range of human brain tumors, including primitive neuroectodermal tumors (PNETs). Transgenic mice expressing T-antigen under the control of the JCV promoter also develop PNETs. In this work we have developed and studied the MR imaging characteristic of these PNET's in a spontaneous JCV T-antigen transgenic mouse brain tumor model at 7 Tesla.

Methods & Materials

MRI scans were performed on seven spontaneous JCV T-antigen transgenic mouse using a vertical, wide-bore magnet at field strength of 7 Tesla, with a Bruker DRX300 console and micro-imaging accessory. Initially pilot scans in the axial, sagittal, and coronal orientations were performed to choose imaging sections to cover the whole brain. Based on these scans an internal anatomic landmark in the mouse brain (Bregma –2) was used to prescribe axial slices perpendicular to this landmark and covering the whole brain. The imaging protocol consists of a T2-weighted spin echo imaging sequence (T_R=2000 msec, T_E=13 msec), Pre–Gad T1-weighted spin echo sequence (T_R=1200 msec, T_E=13 msec), and T2*-weighted spin echo and a 3D gradient echo imaging sequence (T_R=430 msec, T_E=8 msec, Flip angle = 35^0). Other imaging parameters include: FOV = 2.56 x 2.56 x 0.75 cm, acquisition matrix = 256 x 128 x 28, and NEX=4. MR imaging was performed pre- and post- injection with gadolinium, animals were euthanized. Brain tissue was fixed and analyzed by histological staining and immunohistochemistry for the transgene, T-antigen. All of the work described here was done in accordance with protocols approved by the Institutional Animal Care and Use Committee at Temple University and FCCC. A neuroradiologist reviewed all the MR images and characterized the normal and tumor areas of the mouse brain images. This was primarily based on the signal characteristics of the tumor visualization on various imaging sequences used (T2, pre and post T1), as well as morphological characteristics of the normal and abnormal structures in the mouse brain. MR imaging results were correlated with the histological findings.

Results & Conclusion

Figure 1. shows microscopic classification of brain tumors and regions of adjacent normal brain for correlation with radiological findings of PNETs. Excellent correlations between MR imaging and anatomical findings were observed in areas of viable tumor, edema, necrosis, tumor margins, and normal brain tissue. Such a model will be useful for validation of tumor-specific contrast agents and therapeutics for PNETs.

		solid tumor	normal brain	tumor w/ vessels	necrotic	edema	unusual features
CY1861	pre T2	present	present	present	present	present	
	post T1	present	present	not detected	present	present	
CY1885	pre T2	present	present	not detected	not detected	not detected	hemorrhage (arrow)
	post T1	present	present	not detected	not detected	not detected	extra axial tumor mass (asterisk)
CY1915	post T2	not detected	present	not detected	not detected	not detected	contrast enhanced tumor (asterisk)
	post T1	not detected	present	not detected	not detected	not detected	dilated ventricle (arrow)
CY1919	pre T2	present	present	not detected	present	present	lateral ventricle (arrow)
	post T1	present	present	present	present	present	

Table 1. Coregistered features identified by MR Imaging and histological Analysis

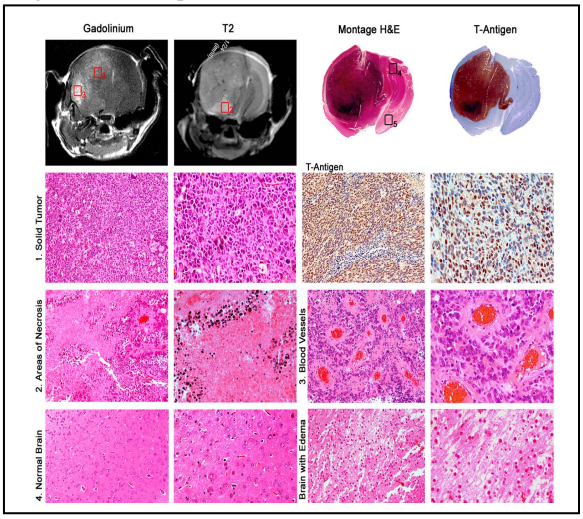

Figure 1: Microscopic classification of brain tumors and regions of adjacent normal brain for correlation with radiological findings.

Representative MR images post gadolinium and pre T2 scanning were used to orient fixed brain tissue for co-registration with histological sections and tissue sections immunostained for the transgene, JCV T-antigen (top row, left to right). Several distinct regions of tumor and brain were observed on both radiological scans and histological sections (labeled as boxes 1 through 5). These regions are shown at low and high magnification. 1. Solid tumor: A large portion of the tumor was homogeneous and highly cellular, labeled as solid tumor. These regions were immunostained with antibody recognizing the transgene, JCV T-antigen and demonstrated strong nuclear signal in the majority of cells (arrow). 2. Necrosis: Distinct areas of necrosis were observed which showed contrast enhancement. 3. Blood vessels: The tumors were highly vascular and large blood vessels (arrow) could be observed in discrete regions of solid tumor. 4. Normal brain: Regions of normal brain tissue were seen which appeared normal. 5. Brain with edema: Regions of normal brain with excess fluid or edema were noted in several animals.

References: Malheiros A, S. M., H. Carrete, Jr., et al. (2003). "MRI of medulloblastoma in adults." Neuroradiology 45(7): 463-7; Rutka, J. T. (1997). Medulloblastoma. Clin Neurosurg 44: 571-85; Zee CS, Segall HD, Nelson M: Infratentorial Tumors in children. Neuroimaging Clinics of North America, 1993; 3(4): 705-714