An Autopsy Brain of Alexander Disease Studied by Comparison of Histology with High Resolution T2*-Weighted MRI at 7T

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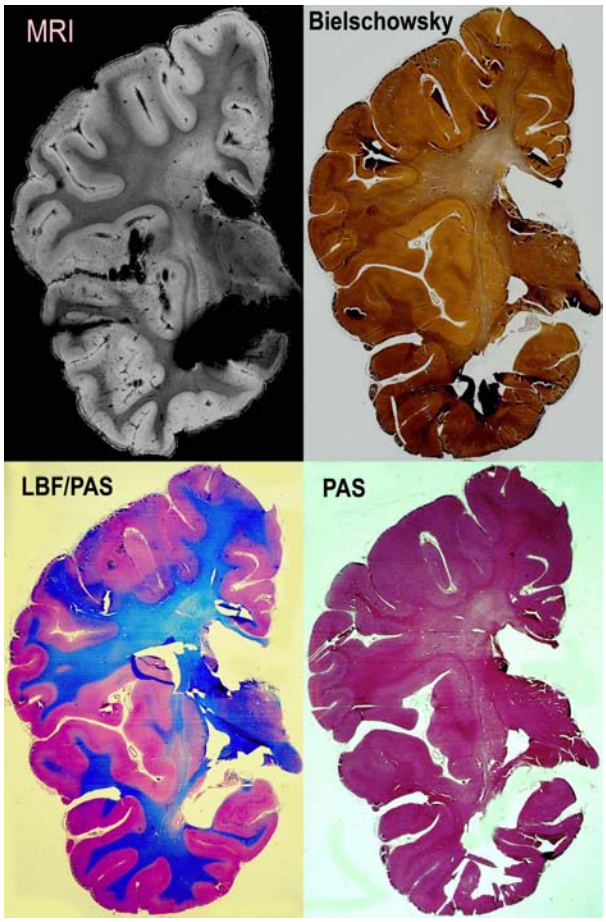
Introduction: In an attempt to establish correlations between histological findings and high resolution T_2*-weighted MRI, brain specimens from a juvenile with Alexander disease was scanned at 3 and 7T. The MRI results were directly compared with histological staining results conducted at the same anatomical location with the whole hemisphere sectioning. Alexander's disease is a rare degenerative disorder of the CNS characterized by diffuse demyelination and rarefaction of the white matter, and widespread accumulation of Rosenthal fibers [1,2]. These fibers are improperly-folded glial fibrillary acidic protein (GFAP), which is the intermediate filament in astrocytes. Alexander disease is the first disease known to be associated with GFAP mutations [1].

Materials and Method: The patient was a diagnosed with Alexander's disease in 1994 and died on August 26th, 2005. Autopsy was performed on following day. The patient had heterozygous mutation in glial fibrillary acidic protein (GFAP) with a C to G mutation at position 1075, predicting amino acid change L359V in 2B domain of GFAP. Brain autopsy and neuropathologic examinations were performed postmortem in the left hemisphere with formalin-fixation. After formalin fixation, MRI studies were conducted using GE Signa 3 and 7T whole-body MRI scanners. Diffusion tensor imaging and T2* mapping at the resolution of 0.8×0.8×0.8 mm^3 were performed at 3T equipped with a 16 channel phase-array detector. The DTI scans were performed using a single-shot EPI in combination with parallel data acquisition method. A DTI scheme with 25 optimized diffusion-weighting directions was used. Whole hemisphere T2*-weighted MRI scans (TE/TR=30/800ms) at the resolution of 160×160×400μm^3 were performed at the 7T equipped with a 24 channel phase-array detector. A modified multi-echo gradient-echo pulse sequence, 2D FAST GRE pulse sequence described elsewhere [3] was used for the 7T. Sectioned specimens were further studied at 7T at the resolution of 78 μm. For further radiological-pathological correlation, conventional H&E stain as well as special staining studies based on Luxol Fast Blue/Periodic Acid Schiff (LFB/PAS) and Bielschowsky methods were performed at Armed Forces Institute of Pathology, where whole brain sectioning facilities are available.

Results and Discussion: The main microscopic finding of the tissue sample with H&E staining is the extensive accumulation of Rosenthal fibers in white matter which confirms the diagnosis of Alexander's disease. Figure 1 shows a set of histological photos developed for the examinations of the neuronal axons density and the level of demyelination together with a T2*-weighted MRI at about the same anatomical location. As shown, the T2*-weighted high-resolution MRI acquired at 7T demonstrated extensive contrast heterogeneity in white matter with patterns which match well with those from histological staining for myelin (LFB/PAS). The T2*-weighted contrast was optimized to enhance sensitivity to microscopic susceptibility in the tissue, which is determined by the iron deposition, myelin content, and axonal structures. Therefore, the hyper-intensity regions in T2*-weighted MRI illustrate lower myelin content and less coherent fiber structures. This notion is confirmed by the fractional anisotropy and quantitative T_2* mapping measured at the 3T (data not shown). The regions with low FA in white matter coincide with the regions with increased T_2* time. The close correlation between T2*-weighted MRI with the histological staining results can be better appreciated by comparing MRI results acquired at even higher resolution with the micrographs of the histological stainings.



Findings from this study suggest that T_2*-weighted MRI at 7T could provide high sensitivity and specificity in identifying white matter disorders. The usefulness of MRI in the diagnosis of Alexander disease suggested in a recent report [2] is further confirmed and strengthened by taking advantage of the close to histologic quality MRI acquired at 7T wih enhanced T2*-weighted contrast. MRI is becoming the powerful modality to study CNS disorders in which biopsy and tissue sampling are challenging. Recent advance in high field technique and multi-channel detection, 7T MRI can achieve high resolution up to 200μm in living human brain. However, it is critical to validate that MRI images reflect the actual disease process. Direct comprison of MRI results with histology of whole mount sections can provide useful information for studying CNS disorders.

References: [1] Brenner M. et al. *Nature genetics* **27**:117, 2001. [2] Marjo S.K. et al. *AJNR* **22**:541, 2001. [3] Li,T.Q. et al. *Neuroimage*, **32**:1032, 2006.