Metabolic abnormalities in perituberous tissue: initial results of a proton MR spectroscopy study of pediatric Tuberous Sclerosis Complex

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INTRODUCTION: Tuberous Sclerosis Complex (TSC), a genetic disorder with an incidence as high as 1/5000, leads to benign tumors in multiple organ systems. It causes epilepsy, autism, and neurocognitive delays. If antiepileptic medication is ineffective, seizures can be abolished with resection surgery if the onset region can be localized. Traditionally, the MRI-defined tuber has been the primary surgery target, but non-tuberous tissue, specifically surrounding an active tuber, may also be epileptogenic. Evidence for this includes: (*i*) patients with persisting epilepsy after tuber resection have improved outcome if perituberous tissue is subsequently removed; (*ii*) animal models and human cases of TSC in which epilepsy occurs in the *absence* of tubers (1). In this study, tubers and normal-appearing tissue were characterized with proton MR spectroscopy (^{1}H-MRS) to test the hypotheses that (*i*) diffuse or (MR-invisible) focal metabolic changes extend beyond the tuber border; (*ii*) the epileptogenic zone, as defined by electro-encephalography (EEG), can be characterized by a unique metabolic profile (biomarker). Since the ^{1}H-MRS was acquired prior to electrode placement and seizure loci cannot be predicted by MRI alone, comprehensive brain coverage was required for retrospective identification of EEG-active regions. To this end, we used three-dimensional ^{1}H-MRS to sample a large (480 cc) volume-of-interest (VOI) at a 1 cc spatial resolution to assess neuronal health, membrane turnover and glial status via their metabolic surrogates *N*-acetylaspartate (NAA), choline (Cho), creatine (Cr) and *myo*-inositol (mI).

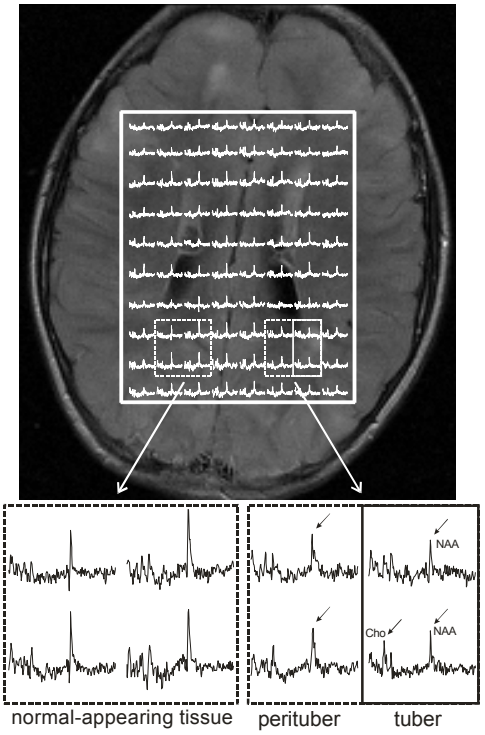

Fig. 1: Real part of the ^{1}H spectra from a tuber, its adjacent tissue (perituber) and contralateral MRI-normal brain. Abnormal resonances (low NAA in both tuber and perituber and high Cho in tuber) are noted with arrows.

METHODS: Four TSC patients referred for epilepsy surgery (2 girls, 2 boys, age range 2-10 years) are currently enrolled. Recruitment is ongoing. Each underwent a standard comprehensive pre-surgical evaluation, which included history and physical examination, video EEG monitoring, MRI scanning, and neuropsychological testing. The study was IRB-approved, informed consent was signed by the parents and assent was obtained from the children where applicable. All scans were done on a Siemens 1.5 T scanner. The ^{1}H-MRS was done as part of a pre-operative MRI protocol, which included MP-RAGE, T2, T2 FLAIR and post-contrast T1. The $10_{AP}\times8_{LR}\times6_{IS}$ = 480 cc ^{1}H-MRS VOI was centered on the corpus callosum and excited with *TE*/*TR* = 26/1800 ms PRESS in 3 sequentially-acquired slabs each with 2nd order Hadamard-encoding in the IS direction. The $16_{AP}\times16_{LR}\times 6_{IS}$ cm^3 field-of-view containing the VOI was partitioned into $1.0_{AP}\times1.0_{LR}\times 1.0_{IS}$ = 1 cc voxels with $16_{AP}\times16_{LR}$ 2D chemical-shift imaging matrix, yielding 480 nominal voxels.

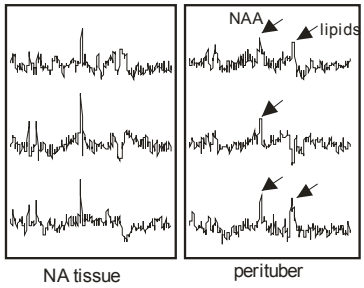

Fig. 2: Real part of the ^{1}H spectra from tissue adjacent to an *active* tuber (perituber) and contralateral normal-appearing (NA) tissue. Arrows denote low NAA and high lipid signal.

RESULTS: Tuber spectra were metabolically abnormal (low NAA, high Cho), as shown in **Figure 1**. Compared to contralateral normal-appearing tissue, spectra from perituberous normal-appearing tissue also showed low NAA (**Figure 1**). In one case, EEG identified an epileptogenic (active) cortical tuber in the parietal lobe; metabolically, its perituberous region was characterized by low NAA and high lipid resonances (**Figure 2**).

CONCLUSION: The initial results suggest that perituberous tissue is metabolically similar to the tubers, which are known loci of seizure activity. This supports other evidence that the dominant epileptogenic zone extends beyond the tuber margin. In addition, the presence of lipid signal in tissue adjacent to an active tuber suggests a possible biomarker for identification of seizure activity.

REFERENCES:

1. Bollo *et al*., Neurosurg. Focus 2008