Prominent citrate predicts malignant progression of low-grade astrocytomas in children

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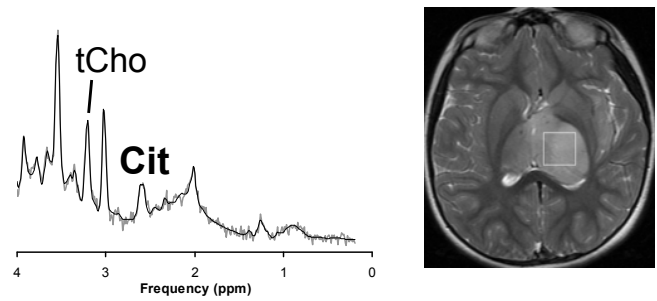
Fig. 1: *Short TE PRESS spectrum and MRI indicating the region of interest of a biopsy-proven grade II astrocytoma at initial presentation. The lesion progressed and the patient died 17 months after initial diagnosis.*
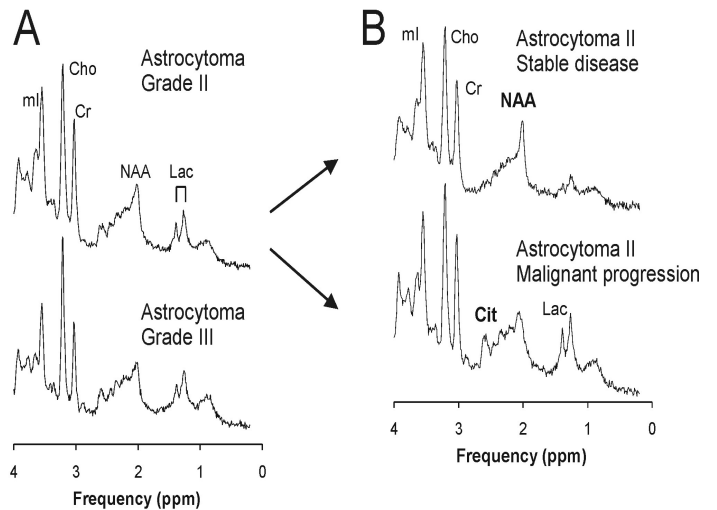
Purpose: To determine whether *aggressive* pediatric low-grade II astrocytoma have metabolic features that distinguishes them from *stable* grade II astrocytoma.

Methods: Medical records and MRS studies of pediatric patients with astrocytomas were retrospectively reviewed. Five patients were identified with *low-grade astrocytomas* (WHO II) and no clinical or radiological progression over at least two years of follow-up (*indolent*-LGA). Six patients were identified with *low-grade astrocytomas* with progression within two years after diagnosis (*aggressive*-LGA). Twelve patients with high-grade (WHO III) astrocytomas (HGA) and poor outcome were also included in this analysis. All *indolent*-LGA subjects were alive whereas all *aggressive*-LGA and HGA subjects have succumbed to their disease at the time of the completion of this study. MR spectra were acquired with single-voxel PRESS (TE=35ms) on a 1.5T MR scanner. Fully automated LC-Model software (S. Provencher, Ontario, Canada) was used to determine absolute concentrations (mmol/kg) of metabolites.

Results: An MR spectrum of a grade II astrocytoma shows a moderate choline (Cho) peak. A signal consistent with citrate (1) is detectable at ≈2.6 ppm (**Fig. 1**). There were no statistical significant differences between all grade II and grade III tumors. Citrate (Cit) was significantly higher in *aggressive*-LGA than in *indolent*-LGA and NAA was lower in aggressive-LGA (**Fig. 2, Tab.**). There was no significant difference in choline between these two subgroups.

Discussion: This study addresses the need to identify markers that would allow pediatric neuro-oncologists to predict which tumors among low-grade (II) astrocytomas have the potential for malignant progression. Elevated citrate in poor outcome LGA may reflect the capability of some LGA to abnormally increase glycolysis to support increased proliferation (Warburg effect). Lower NAA is consistent with a lower density of residual normal neurons/axons within aggressive-LGA. Albeit, Cho is generally higher in higher grade lesions, it did not correlate with outcome. The above observations are consistent with recent MRS findings in pontine gliomas. Pontine gliomas, often low-grade at diagnosis, but then with inevitable progression and 100% mortality generally show high citrate levels whereas Cho levels are moderate (1,2).

Fig. 2A: *Averaged spectrum of all grade II (upper trace) and all grade III astrocytoma (lower trace).* **2B:** *When low-grade astrocytomas were subdivided according to clinical outcome, citrate (Cit) and N-acetyl-aspartate (NAA) were significantly different. Cr = creatine, mI = myo-inositol.*

Table: Concentrations (mmol/kg) of pediatric astrocytomas.

	Astrocytomas with stable disease	Astrocytomas with disease progression within two years after initial diagnosis	
	Grade II (n=5)	Grade II (n=6)	Grade III (n=12)
[Cit]	0.6±0.4	4.1±1.2**	3.2±2.7*
[NAA]	3.2±0.8	0.6±0.7**	1.6±0.8*
[Cr]	7.1±1.5	7.6±3.2	6.1±2.3
[tCho]	3.0±1.3	3.5±1.3	3.7±1.8
[a][Lac]	1.1±0.9	4.8±4.4	2.5±2.3

*p<0.01, **p<0.001 versus *indolent*-LGA, [a]Lac conc. is reported in mmol/liter volume.

Conclusion: Elevated citrate and low NAA may predict malignant progression of low-grade astrocytomas.

References: 1.Seymour et al. AJNR 29: 1006-1011, 2008. 2. Panigrahy et al. Neuro Oncol 10:32-44, 2008.