

Citrate in Pediatric CNS Tumors

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Introduction: We have observed a signal consistent with citrate (Cit) in MR spectra of pediatric brain tumors. The goals of this study were to determine (a) the prevalence and concentration of citrate in various tumors and (b) changes of Cit in progressing lesions.

Methods: Short echo time (35ms) single-voxel PRESS spectra from 85 pediatric patients (Tab. 1) were analyzed. The lesion of one patient was studied with three different echo times. For peak assignment, *in vivo* spectra were compared with spectra obtained from a model solution of citrate. Spectra from the citrate solution were added to the basis-set of the LCMoDel software (Stephen Provencher Inc., Oakville, Ontario, Canada, LCMoDel Version 6.1-4F) for absolute quantitation. Citrate concentrations and the Cramer-Rao lower bounds (CRLB), objective indicators for the reliability of detection and quantitation, were analyzed.

Results: Citrate with CRLB<25% was detected in 26 of 85 patients. Diffuse intrinsic brain stem glioma (DIBSG) had the highest mean concentration and the highest prevalence (Figs. 1+2, Tab. 1). There was only little evidence for citrate in low grade pilocytic astrocytoma. A significant reduction of citrate was observed in six DIBSG that had follow-up MRS after radiation therapy (Fig. 3).

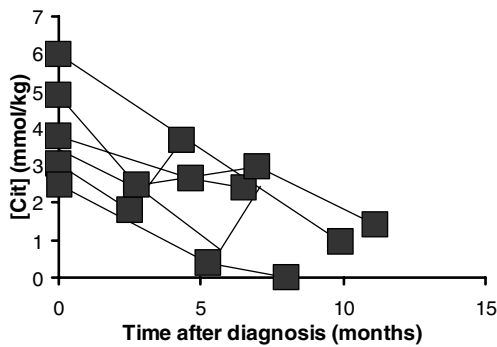


FIG. 3: Citrate levels decreased over time in six DIBSG patients with follow-up MRS after radiation therapy ($p<0.01$, one sample *t*-test of slopes of linear regressions). DIBSG are believed to progress from low-grade gliomas to high grade lesions.

Discussion: Citrate has been previously detected *in vivo* in prostate tissue. Declining levels of citrate is an important marker for prostate cancer (1, 2). In this study, Cit was highest in DIBSG at baseline. DIBSG are believed to transform rapidly from low-grade gliomas to more malignant tumors, usually classified as glioblastoma at autopsy (3-6). Our data suggest that malignant transformation is accompanied by decreasing citrate levels.

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References: 1. Kurhanewicz, J., et al. *Magn Reson Med*, 1993. 29(2): p. 149-57. 2. Kurhanewicz, J., et al. *Urology*, 1995. 45(3): p. 459-66. 3. Farmer, J.P., et al. *Pediatr Neurosurg*, 2001. 34(4): p. 206-14. 4. Nelson, M.D., Jr., et al. *Radiology*, 1994. 191(1): p. 279-82. 5. Yoshimura, J., et al. *Neurol Med Chir (Tokyo)*, 2003. 43(8): p. 375-82; discussion 382. 6. Pan, E., et al., *Brainstem Gliomas*, in *Pediatric CNS Tumors*, N. Gupta, D. Haas-Kogen, and A. Banerjee, Editors. 2004, Springer-Verlag: Berlin Heidelberg New York. p. 49-61.

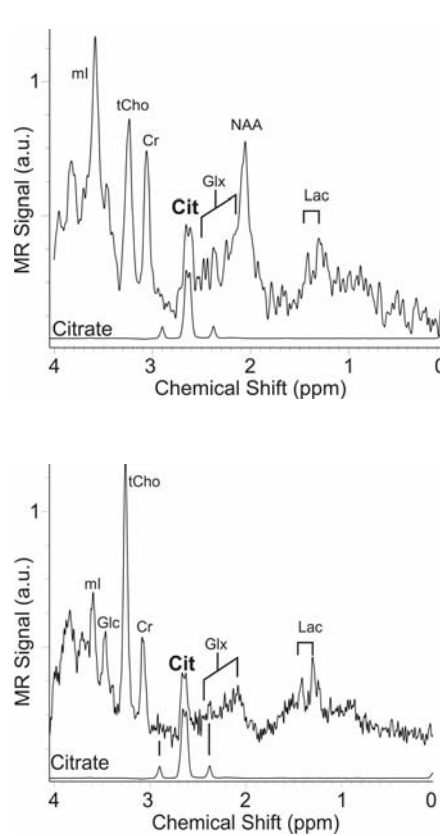


FIG. 1: *In vivo* spectra of a diffuse intrinsic brain stem glioma (top) and an anaplastic astrocytoma (bottom). A complex signal centered at 2.6 ppm consistent with the spectrum of a citrate solution was observed.

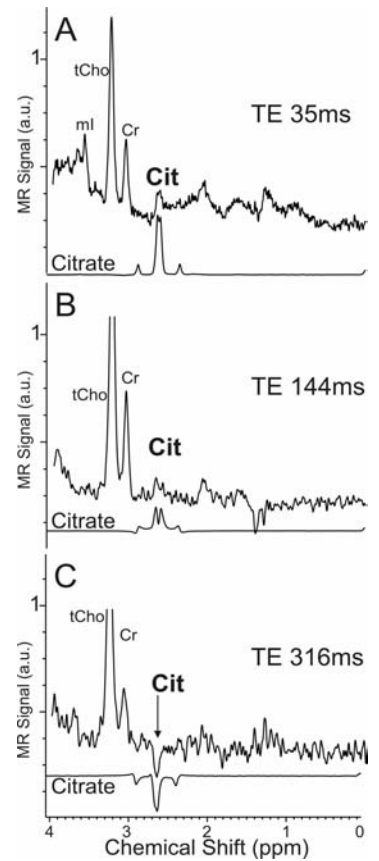


FIG. 2: The complex signals centered at 2.6 ppm in tumor spectra and in a model solution of citrate show the same J-modulation.

TAB. 1: Citrate concentrations (mmol/kg) and prevalence in common pediatric CNS tumors

	DIBSG	A/AA	E/AE	MBL	PA
Subjects	12	14	14	22	23
[Cit]	4.0±1.1	2.6±1.8	2.9±2.2	1.9±1.2**	1.4±1.1***
Cit CRLB	0.22±0.07	0.37±0.25	0.46±0.67	0.56±0.37**	0.64±0.37***
#CRLB < 25%	67%	36%	36%	28%	13%

*Represents significance compared to DIBSG: ***, $p<0.0001$; **, $p<0.001$; *, $p<0.01$. DIBSG = Diffuse intrinsic brain stem glioma, A/AA = Regular and anaplastic astrocytoma, E/AE = regular and anaplastic ependymoma, MBL = medulloblastoma, PA = pilocytic astrocytoma. CRLB = Cramer-Rao lower bounds. #CRLB<25% = number of subjects where CRLB for Cit was less than 25%.