Quantitative MR Spectroscopy of Diffuse Intrinsic Brain Stem Glioma

A. Panigrahy[1], M. D. Nelson[1], J. L. Finlay[2], and S. Bluml[1,3]

[1]Dept. of Radiology, Childrens Hospital Los Angeles, Los Angeles, CA, United States, [2]Cancer and Blood Diseases, Childrens Hospital Los Angeles, Los Angeles, CA, United States, [3]Rudi Schulte Research Institute, Santa Barbara, CA, United States

Introduction: Among pediatric brain tumors, diffuse intrinsic brain stem gliomas (DIBSG) carry the worst prognosis. DIBSG are inoperable and highly resistant to chemo- and radiation therapy. Mean survival after diagnosis is less than 12 months and there has been no improvement over the last several decades (1-7). At diagnosis most DIBSG present as low- or high-grade astrocytoma. At autopsy most lesions have progressed to glioblastoma (1-5, 8). Progress in the development of therapies for DIBSG is compromised by the unavailability of tissue samples and the lack of non-invasive markers to characterize disease status. The purpose of this study was to compare the metabolic profile of DIBSG with that of astrocytoma elsewhere in the central nervous system and to determine whether the measurement of metabolic features can improve the assessment of disease status.

Methods: 40 *in vivo* MR spectroscopy (MRS) studies of 16 patients with DIBSG at baseline and after radiation therapy were retrospectively reviewed. Control data for baseline studies of DIBSG were obtained from 14 untreated regular and anaplastic astrocytomas and 12 age-matched subjects with normal brain stem. All spectra were acquired with PRESS, TE=35 ms. Absolute metabolite concentrations (mmol/kg) and lipid intensities (arbitrary units) were determined using LCModel software (Stephen Provencher Inc., Oakville, Ontario, Canada, LCModel Version 6.1-4F). Medical records were reviewed to determine the time of disease progression after radiation therapy. *Metabolic disease progression* in individual subjects was defined by increased absolute concentrations of total choline (tCho) – indicating increasingly proliferative tumors (9-19). LCModel processing software provides concentrations and the Cramer-Rao lower bounds (conc. ± CRLB) for each metabolite of a spectrum. A change of tCho was concluded when there was no overlap between two consecutively measured tCho concentrations ± CRLB.

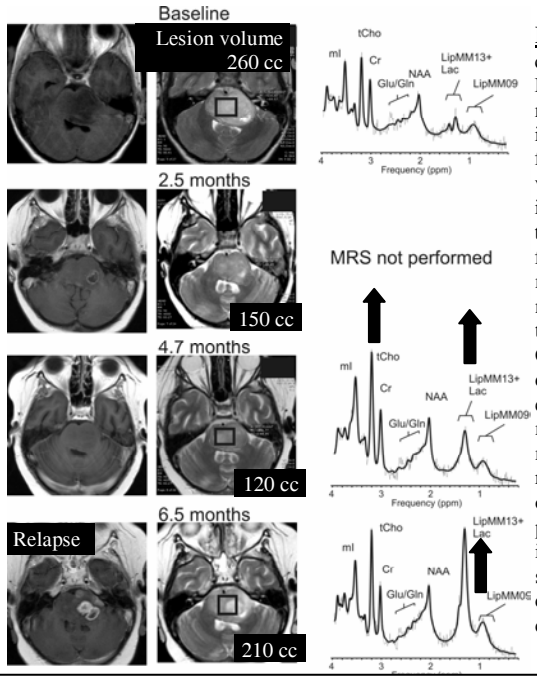

FIG. 1: Transverse post-contrast T1w, T2w MRI, and MRS of patient 3. The metabolic progression observed in this patient was representative for most patients. Lesion volume on MRI decreased from initially 260 to 150 cm^3 after therapy at 2.5 months and then further to 120 cm^3 at 4.7 months. At that time it was noted that MRS, with increased tCho, lipids, and reduced Cr/tCho, was suggestive of disease progression. A ring enhancing lesion detected at 2.5 months was not observed at 4.7 months. Clinical and radiological deterioration occurred at 6.5 months and this patient died 11 months after initial diagnosis. Spectra are scaled to measured concentrations to allow direct comparison of peak areas.

TAB 1: Absolute concentrations (mmol/kg tissue, mean± standard deviation) and metabolite ratios

	age	NAA	Cr	**tCho**	[b]LipMM09	[b]LipMM13	NAA/tCho	Cr/tCho
DIBSG	7.0±2.6	2.6±0.9	4.3±1.1	**1.9±0.7**	5.5±3.0	6.5±10	1.6±0.6	2.3±0.6
A/AA	10.3±5.6	2.4±1.6	7.5±1.9**	**4.2±2.6***	8.9±3.7	8.6±7.8	0.8±0.7	2.2±1.1
[c]Control	6.7±4.1	9.6±1.6***	5.2±0.4*	**2.7±0.3***	5.7±2.0	1.3±0.8*	3.6±0.7***	1.9±0.3

Notes: -*p<0.01, **p<0.001, ***p<0.0001 versus DIBSG (Kruskal-Wallis rank-sum test). [b]absolute intensity, [c]Brain Stem. A/AA = regular astrocytoma and anaplastic astrocytoma.

Results: At baseline, creatine and tCho were significantly lower in DIBSG than in astrocytoma elsewhere in the central nervous system. tCho in DIBSG was also significantly lower than in normal brain stem (**Tab. 1**). Serial MRS in DIBSG revealed increasing levels of tCho ($p<0.05$) and lipids ($p<0.05$) and reduced ratios of NAA, creatine, and myo-inositol relative to tCho (all $p<0.01$) (**Fig. 1**). Metabolic disease progression preceded clinical deterioration (**Fig. 2**).

Discussion: Low tCho of DIBSG at baseline is consistent with low proliferative tumors. Subsequent metabolic changes that have been associated with malignant degeneration preceded clinical deterioration. MRS provides early surrogate markers for disease progression and may be an important tool to characterize response to therapy and tumor progression. This may compensate for the small number of patients available for studies, and allow a faster completion of clinical trials accelerating the development of effective therapies.

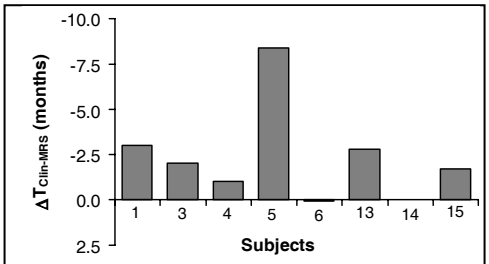

FIG. 2: Clinical deterioration and metabolic disease progression
Shown is the difference between the time of clinical deterioration and metabolic disease progression. Due to the limited number of follow-up MRS studies carried-out this comparison was limited to eight subjects. MRS changes preceded clinical deterioration in six patients and coincided in two patients (mean = -2.4±2.7, $p<0.04$, one-sample two-sided t-test).

Acknowledgment: U01 CA97452-02 (Natl. Childhood Cancer Foundation) and PBTF-US

References: 1. Farmer, J.P., et al.. Pediatr Neurosurg, 2001. 34(4): p. 206-14. 2. Freeman, C.R., et al.. Int J Radiat Oncol Biol Phys, 1998. 40(2): p. 265-71. 3. Mandell, L.R., et al.. Int J Radiat Oncol Biol Phys, 1999. 43(5): p. 959-64. 4. Nelson, M.D., Jr., et al.. Radiology, 1994. 191(1): p. 279-82. 5. 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. 6. Rubin, G., et al.. Childs Nerv Syst, 1998. 14(4-5): p. 167-73. 7. Hargrave, D., et al.. Lancet Oncol, 2006. 7(3): p. 241-8. 8. Yoshimura, J., et al.. Neurol Med Chir (Tokyo), 2003. 43(8): p. 375-82; discussion 382. 9. Negendank, W.G., et al.. J Neurosurg, 1996. 84(3): p. 449-58. 10. Negendank, W.G.. NMR in Biomedicine, 1992. 5: p. 303-324. 11. Astrakas, L.G., et al.. Clin Cancer Res, 2004. 10(24): p. 8220-8. 12. Stadlbauer, A., et al.. Radiology, 2006. 238(3): p. 958-69. 13. Shimizu, H., et al.. AJNR Am J Neuroradiol, 2000. 21(4): p. 659-65. 14. Tamiya, T., et al.. Neuroradiology, 2000. 42(5): p. 333-8. 15. Li, X., et al.. NMR Biomed, 2004. 17(1): p. 10-20. 16. Wang, Z.J., et al.. Neuroimaging Clin N Am, 1998. 8(4): p. 781-807. 17. Laprie, A., et al.. Int J Radiat Oncol Biol Phys, 2005. 62(1): p. 20-31. 18. Howe, F.A., et al.. Magn Reson Med, 2003. 49(2): p. 223-32. 19. Tedeschi, G., et al.. J Neurosurg, 1997. 87(4): p. 516-24.