Proton MRSI Biomarkers Predict Survival in Children with CNS Tumors

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Introduction

Central nervous system (CNS) tumors in children differ from those seen in adults in terms of histology and children with CNS tumors are surviving longer (1). A consistent approach to the postoperative evaluation and follow-up of these children is missing despite advances in patient management (2). Since their frequent adjacent location to crucial structures limits diagnostic biopsy, modern diagnostic imaging techniques were developed to detect these tumors safely and accurately but with less specificity (3). Proton Magnetic Resonance Spectroscopic Imaging (MRSI) promises to provide accurate, sensitive and specific biomarkers of outcome (4). The objective of this study was to test the hypothesis that combining information from biologically important intracellular molecules, obtained by proton MRSI and histology, will increase the probability of predicting survival in children with pediatric CNS tumors.

Materials and Methods

Proton MR spectroscopic imaging exams were performed on 76 children with neuroepithelial brain tumors prior to therapy on a 1.5-T MR system. Proton MR spectroscopic imaging was performed using multi-voxel chemical shift imaging (CSI) with point resolved spectroscopy (PRESS) and volume preselection. The following acquisition parameters were used: TR=1s, TE=65msec, 16x16 phase encoding matrix, 160 mm FOV, slice thickness of 10 mm, 1250 Hz spectral width, 2 averages and 512 points. Data sets of 1-1.2 cc nominal resolution were obtained. Data processing was performed on a Sun workstation using analysis software by General Electric (SAGE) and in-house developed software using IDL 5.3. Patients who died (n=18) and those alive (n=58) were compared with respect to median (interquartile range) levels of choline and lipids/lactate using the Mann-Whitney U-test. Association between WHO grade and survival was determined by chi-square. Area under the ROC curve was calculated as a measure of diagnostic performance for choline and lipid/lactate in differentiating patient survival (5). Multiple stepwise logistic regression analysis was applied to identify independent predictors of survival considering choline, lipid/lactate, and WHO grade (low versus high grade tumors).

Results

ROC curve analysis indicated that discrimination of survival outcome for both choline (AUC = 0.725, 95% confidence interval = 0.600 – 0.859) and lipid/lactate (AUC = 0.687, 95% confidence interval 0.544 – 0.830). Multiple stepwise logistic regression analysis indicated that among choline, lipid/lactate, and WHO grade, only choline was an independent predictor of survival (likelihood ratio test = 9.64, P = 0.002). Lipid/lactate (P = 0.16) and WHO grade (P = 0.58) provided no additional information in differentiating alive vs. dead outcome beyond that provided by choline.

Variable	Alive (n = 58)	Dead (n = 18)	P value
Choline	1.08 (0.85 – 1.60)	1.70 (1.20 – 2.58)	0.004*
Lipid/lactate	0 (0 – 1.23)	1.75 (0.22 – 3.07)	0.012*
WHO grade			0.05*
Low (1 or 2)	43 (74%)	9 (50%)	
High (3 or 4)	15 (26%)	9 (50%)	

Data represent median with interquartile range in parentheses. *Statistically significant.

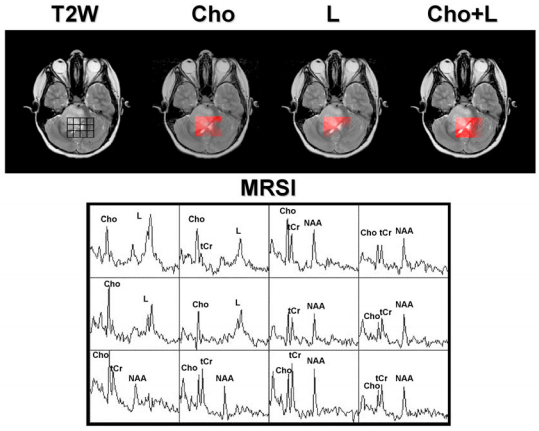
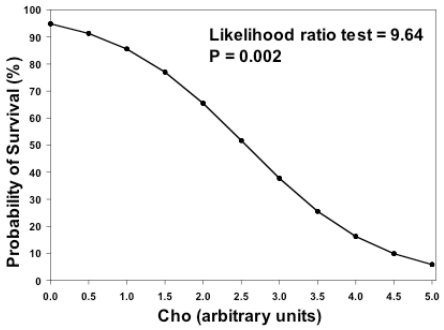


Figure 1: MRI and proton MRSI on a 9-year-old girl with a poorly differentiated malignant neoplasm, PNET, prior to treatment. T2-weighted (T2W) image shows a pontine mass of high T2. The grid overlay on the T2W image shows the anatomic locations for the simultaneous MRSI spectral acquisitions from multiple locations in one slice. Despite this challenging location for biopsy and proton MRSI, the MR spectra exhibit three prominent and well-resolved peaks of biological importance in normal brain tissue, NAA (n-acetylaspartate), tCr (total creatine pool), and choline-containing compounds (Cho). The Cho, L, and Cho+L metabolite images have been overlaid on the T2W image and show metabolite distributions. The Cho image depicts the distribution of high Cho, due to altered phospholipids metabolism. The L image shows the distribution of primarily mobile lipids (probable contribution from lactate), possibly due to cellular death. The combined Cho+L image thus depicts altered phospholipid metabolism and cellular death, both characteristic of malignant transformation in a high-grade tumor.

The predicted probability of survival based on choline level is shown in the following table and figure.

Choline	Probability of Survival
0.5	92
1.0	86
1.5	77
2.0	65
2.5	50
3.0	38
3.5	25
4.0	16
4.5	10



Discussion

Our data suggest that proton MRSI-derived measures of Cho and lipids and/or lactate in combination with the gold standard of diagnosis, histology, may be valuable in predicting patient survival. Thus, MRSI biomarkers for predicting survival is an excellent test in children, especially if diagnostic biopsy is not feasible. Proton MR spectroscopic imaging indices may aid in the diagnosis and help facilitate development of therapies tailored to the biological behavior of the tumor.

References

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