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Detection and characterization of neurotoxicity in cancer patients using proton MR spectroscopy

Emilie A. Steffen-Smith, BA¹, Pamela L. Wolters, PhD^{1,2}, Paul S. Albert, PhD³, Eva H. Baker, MD, PhD⁴, Kim C. Shimoda, PhD⁵, Alan S. Barnett, PhD⁶, and Katherine E. Warren, MD¹

¹ Pediatric Oncology Branch, National Cancer Institute, Center for Cancer Research, National Institutes of Health (NIH), Bethesda, MD

² Medical Illness Counseling Center, Chevy Chase, MD

³ Biometric Research Branch, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, MD

⁴ Clinical Center, National Institutes of Health, Bethesda, MD

⁵ Children's National Medical Center, Washington, DC

⁶ National Institute of Mental Health, CBDB, National Institutes of Health, Bethesda, MD

Abstract

Objective—The study objective was to detect abnormalities and identify relationships between brain metabolic ratios determined by proton magnetic resonance spectroscopic imaging (¹H-MRSI) and neuropsychological (NP) function in cancer patients at risk for neurotoxicity.

Methods—Thirty-two patients received ¹H-MRSI using a multi-slice, multivoxel technique on a 1.5T magnet. Cho/NAA, NAA/Cr and Cho/Cr ratios were identified in 7 pre-determined sites without tumor involvement. A battery of age-appropriate NP tests was administered within 7 days of imaging. Relationships were examined between test scores and metabolite ratios.

Results—¹H-MRSI data was considered acceptable in 31 patients. Significant associations were identified. Full Scale IQ ($r = -0.62$, $p = 0.011$), Verbal IQ ($r = -0.61$, $p = 0.014$), Performance IQ ($r = -0.57$, $p = 0.024$), and arithmetic scores ($r = -0.51$, $p = 0.50$) correlated with Cho/Cr in the globus pallidus. Full Scale IQ ($r = -0.48$, $p = 0.043$) correlated with Cho/NAA in the putamen. Reading scores correlated with NAA/Cr in the putamen ($r = 0.59$, $p = 0.034$). Presence of a lipid peak (1.6 – 1.8 ppm) was associated with lower Full Scale IQ ($p = .012$) and Verbal IQ scores ($p = .004$).

Conclusions—This study identifies relationships between brain metabolite ratios and cognitive functioning in cancer patients. ¹H-MRSI may be useful in early detection of neurotoxic effects, but prospective longitudinal studies in a homogeneous population are recommended to determine the prognostic value.

Keywords

MRI; MRS; Primary brain tumor; Pediatric; Neuropsychological assessment

Please send all correspondence to: Katherine E. Warren, M.D. Pediatric Oncology Branch National Cancer Institute Building 10/Room 1–3940 9000 Rockville Pike Bethesda, MD 20892 Phone: 301–435–4683 FAX: 301–451–7052 Email: warrenk@mail.nih.gov.

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Introduction

Neurotoxicity (NT) is a significant treatment complication for many cancer patients, but little is known about its etiology and early objective detection is difficult. Cognitive deficits documented by neuropsychological (NP) testing involve attention and concentration, processing speed, memory, general intelligence, language, and academic achievement [29, 26,13]. Risk factors identified from studies of patients with acute lymphoblastic leukemia and brain tumors include young age at treatment [13,23,3,1], dose and type of treatment, particularly cranial irradiation and high-dose chemotherapy [13,15,25], increased time since treatment [26,23], and female gender [3]. Structural changes, including subacute leukoencephalopathy, mineralizing microangiopathy, and cortical atrophy, have been observed on CT or MRI during and after treatment [5], but associations between NP deficits and structural abnormalities are inconsistent and yield mixed results [18,28]. Early detection and improved objective characterization of NT would be useful in the clinical management of these patients.

Proton magnetic resonance spectroscopy (MRS) is a noninvasive technique used to assess regional biochemical activity *in vivo* and can detect changes in the brain in the absence of detectable abnormalities on standard MRI [6]. Principal metabolites in the brain identified using MRS techniques with long echo times (TE; 135–270ms) include N-acetyl aspartate (NAA), free choline and choline containing compounds including phosphocholine and glycerophosphocholine (Cho), and creatine and phosphocreatine (Cr) (Figure 1) [22]. Proton magnetic resonance spectroscopic imaging (¹H-MRSI) is a multi-voxel, multi-slice technique that allows simultaneous acquisition of metabolite data from multiple areas of the brain. The purpose of this study was to explore relationships between NP function and metabolite ratios of specific brain regions using ¹H-MRSI.

Methods

Patients

Eligible patients had a brain tumor, received high-dose systemic chemotherapy, intrathecal chemotherapy, or cranial radiation, or had documented or suspected clinical neurotoxicity related to cancer or its treatment. The study was approved by our institution's review board, and informed consent was obtained from all patients or their legal guardians.

MRI and ¹H-MRSI

Patients received ¹H-MRSI on a 1.5T whole body imager (Signa; GE Medical Systems, Milwaukee, WI) equipped with self-shielded gradients and a standard quadrature head coil. Spectroscopy data for metabolites of interest was acquired using a multi-slice, multi-voxel technique using a chemical shift-selective (CHESS) saturation pulse for water suppression and eight outer volume saturation (OVS) bands for lipid signal suppression. Four 15mm thick axial slices were acquired (repetition time 2300 ms, TE 272 ms, 32×32 phase encoding steps over 240mm field of view) [12]. Spectral data were recorded simultaneously for each slice from multiple voxels, each with a nominal volume of 0.84 cm³ (1.5cm × .75cm × .75cm). Acquisition time was approximately 20 minutes. Following ¹H-MRSI acquisition, T2-weighted axial fluid attenuated inversion recovery (FLAIR) images were obtained using the same field of view and angulations to ensure co-registration with ¹H-MRSI.

¹H-MRSI Analysis

Spectroscopy data were analyzed on a Sun Workstation (Sun Microsystems, Mountain View, CA) with a customized software package using IDL data processing language (Research Systems, Inc, Boulder, CO). Relative areas under the NAA, Cho, and Cr peaks were determined

bilaterally at eight pre-determined regions of interest (ROIs) not involved by the tumor. These were chosen based on their involvement in the selected domains of cognitive function (Figure 2): frontal grey matter (FGM), frontal white matter (FWM), occipital parietal white matter (OPWM), thalamus (THAL), globus pallidus (GP), putamen (PUT), caudate head (CH) and hippocampus (HIPPO). Semi-quantitative analysis was performed for each ROI, integrating the area under the signal intensity peak for each metabolite as a surrogate for relative metabolite concentrations [12].

Spectroscopic data from ROIs were accepted or rejected based on several criteria including Cr and Cho peak separation and signal-to-noise ratio [12]. Additional exclusion criteria included tumor involvement, interference from tissue due to shunt or other surgical intervention, and overlap of other brain structures in ROI voxels. Areas under the peaks were normalized using ratios: Cho/NAA, NAA/Cr, and Cho/Cr. Presence of an abnormal lipid peak (1.6 – 1.8 parts per million, ppm) in any brain area as identified in previous analysis [37] was also recorded.

Neuropsychological Testing

Within one week of imaging, patients were administered an age-appropriate battery of NP tests assessing seven main cognitive domains: general intelligence, language, visual-perceptual skills, memory, processing speed, executive function, and academic achievement. General intelligence, language, and visual perceptual skills were assessed with the Wechsler Abbreviated Scale of Intelligence (WASI) [27] for the majority of patients ages 6 years and older or the Wechsler Preschool and Primary Intelligence Scale-Revised [41] for children ages 2.6 to 5.11 years. The California Verbal Learning Test (CVLT) for children (CVLT-C; 6 – 16.11 years) [10] or the CVLT for adults (CVLT-II; ≥ 16 years) [11] were administered to evaluate overall verbal memory and delayed recall. Immediate auditory memory was assessed using the Numerical Memory subtest of the McCarthy Scales of Children's Ability [20] (2.5 – 6 years), or the Digit Span subtest of the Wechsler Scale of Intelligence for Children-Third Edition (WISC-III; 6 – 16.11 years) [40] or the Wechsler Adult Intelligence Scale—Third Edition (WAIS-III; ≥ 16 years) [49]. Processing speed was evaluated using the WISC-III or WAIS-II subtests (Symbol Search and Coding), which comprise the Processing Speed Index. Trailmaking Test-Part B [30] (≥ 8 years) was administered as a measure of executive function. Academic achievement (reading/arithmetic) was assessed using the Wide Range Achievement Test-Third Edition (WRAT-3; ≥ 5 years) [38]. From these tests, ten primary scores were selected for comparison with ^1H -MRSI data. Table 1 presents the NP tests and primary scores used in analysis for each domain.

Statistical Analysis

Spearman rank correlations were used to estimate the relationships between metabolite ratios in each ROI and NP test scores. Student's t-tests were used to compare differences in test scores for patients with or without an abnormal lipid peak. Given the exploratory nature of this study, corrections for multiple comparisons were not applied. Two-sided P values less than or equal to 0.05 were considered significant, and suggestive of future confirmation.

Results

Patients

^1H -MRSI and NP testing were performed in 32 patients. One patient was excluded from analysis due to movement during image collection, which interfered with the ^1H -MRSI spectra quality. Of the remaining 31 patients, 17 were male and 14 were female. The mean age of subjects was 12.4 years (median 10.4 years, range 2.4 – 40.5 years). Diagnoses included primary CNS tumors ($n = 20$), acute lymphoblastic leukemia ($n = 9$), and osteosarcoma ($n = 2$). Mean age at diagnosis was 7.7 years (median 6.4 years, range 1.3 – 37.9 years). Due to

cross-sectional design, time since diagnosis at enrollment varied greatly across the sample (mean 4.7 years, median 2.9 years, range 0.2 – 32.9 years).

¹H-MRSI

Regions of interest were examined bilaterally. Therefore, sixty-two spectra were examined for each of the eight ROIs. MRIs were reviewed by a neuroradiologist (E.B.). Of the 31 patients, 11 patients had abnormal MRI findings such as atrophy, leukomalacia, or diffuse white matter changes. Spectra from voxels involving tumor were excluded from analysis. Data from the caudate head were excluded as less than half of spectra were acceptable for analysis. Table 2 summarizes the characteristics of the accepted spectra for the remaining 7 ROIs.

Neuropsychological Test Results

As listed in Table 1, mean scores for the majority of the tests were within one standard deviation below the normative mean (Average to Low Average Range). The mean score for the time to complete the executive function test was almost two standard deviations slower than the normative mean (Borderline Range). However, these patients demonstrated a wide range of functioning from Deficient to Very Superior on all measures except for the executive function test, which ranged from Deficient to High Average.

Relationships between NP function and ¹H-MRSI

Table 3 provides the correlations between NP testing and metabolite ratios with $p \leq 0.05$. An abnormal lipid peak (1.6 – 1.8 ppm) (Figure 3) was identified in 13 patients, 11 of whom reported symptoms of NT. Locations of the peak varied. Patients with a lipid peak ranged in age from 4.1 to 37.4 years (mean 12.6 years, median 9.9 years). Time since diagnosis ranged from 0.4 to 32.9 years (mean 7.0 years, median 3.8 years). Patients were divided into subgroups of those with the abnormal lipid peak ($n = 13$) and those without ($n = 18$). Difference in mean test scores for those with the abnormal peak and those without were assessed for all NP tests. Differences in VIQ and FSIQ scores between groups were significant ($p = 0.004$ and $p = 0.012$, respectively) (Figure 4).

Discussion

NT is a poorly characterized, but frequent consequence, of cancer related therapy, and the pathophysiology remains largely unknown. Most of the previous studies evaluating the neurotoxic effects of treatment on cancer patients have concentrated on structural or functional changes. Studies examining relationships between NP testing and structural changes on MRI have yielded inconsistent results. A noninvasive method for early detection of structural changes that correlates with NP function would be clinically useful in the management of these patients. Proton magnetic resonance imaging is a relatively recent clinical advance that has proven useful in the evaluation of neoplasms [32] and central nervous system diseases such as white matter disease [34,16,4], Alzheimer's disease [36], and attention deficit/hyperactive disorder (ADHD) [14]. The relationship between metabolic profiles in proton MRS and NP function has not been well-characterized. Previous research on NP function and proton MRS has applied single voxel techniques [8,9]. This study describes relationships between cognitive function and multi-voxel ¹H-MRSI metabolic data in cancer patients.

NAA, an amino acid derivative found predominantly in neurons [35], is considered a marker of neuronal integrity and implicated in cognitive function [43]. NAA is reduced in pathological states with neuronal loss or injury such as brain tumor [32], head trauma [17], and infection [7]. Phosphocholine and glycerophosphocholine are known precursors of cell membrane synthesis and components of membrane breakdown products [22]. Increased Cho is associated with membrane turnover and reflects cellular density [21]. Lactate (Lac) and lipids (Lip) are

also detectable at long TEs but are not seen in normal brain tissue [31]. Lac is a reflection of anaerobic metabolism. Prominent lipid peaks have been reported in MRS studies of multiple sclerosis [33], Tay-Sachs disease [2], and Sjögren-Larsson syndrome [42,24] and are attributed to demyelination or membrane breakdown. Because neuronal loss and demyelination have been associated with NT, we hypothesized that changes in the metabolites that reflect these conditions would be markers of NT.

In this study, metabolite ratios (Cho/Cr, Cho/NAA, and NAA/Cr) were compared to NP test results. We investigated areas of the brain that are known to be involved in selected domains of NP function. Relationships between ¹H-MRSI metabolite ratios and lower NP functioning were identified in this study. IQ appears to be the most robust measure for ¹H-MRSI comparisons. Comparisons between metabolite ratios in subcortical regions and lower IQ scores yielded significant relationships. Increased levels of choline or lipids, both reflections of membrane turnover or demyelination, are related to lower IQ scores and overall cognitive deficits. This metabolic profile has been observed in other patient groups who present with decreased cognitive function, including patients with head trauma [17] or white matter disease [34,16,4]. Studies using proton MRS techniques to evaluate patients with traumatic brain injury and HIV disease have also shown that decreased NAA, indicating either neuronal loss or dysfunction, is associated with poor cognitive outcome [17,19]. In patients with Tay-Sachs disease and Sjögren-Larsson syndrome [24], populations at risk for impaired cognitive function, memory and executive function [44], increased levels of choline and prominent lipid peaks have been observed and associated with active demyelination [2,44] and white matter abnormalities. The relationships identified between poorer NP function and metabolite ratios in our study may reflect changes in myelin metabolism that are not consistently perceptible on MRIs.

The development of NT in cancer patients is variable with regards to clinically detectable onset. When these changes in metabolites and detection of lipid peaks develop in relation to treatment remains to be determined. A prospective, longitudinal study may yield additional information about this unique metabolic profile and its relationship to NP function.

This study shows that ¹H-MRSI is a potential tool for early identification of neurological and NP complications in cancer patients. Limitations of this study include cross sectional design, small sample size, multiple comparisons, and heterogeneous population. Thus, our findings will need to be confirmed in additional studies. Further studies using ¹H-MRSI and NP assessment are warranted to determine if this method can be used to noninvasively identify, predict, and better characterize NT.

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Figure 1. Normal spectrum

Normal spectrum (repetition time 2300 ms, echo time 272 ms) from frontal grey matter in 20yo female patient.

Figure 2. Regions of Interest

Pre-determined regions of interest for ^1H -MRSI analysis. 1. Frontal grey matter, 2. Frontal white matter, 3. Occipital parietal white matter, 4. Thalamus, 5. Putamen, 6. Globus Pallidus, 7. Caudate head, and 8. Hippocampus.

Figure 3. Identification of the lipid peak

¹H-MRSI results from left occipital parietal white matter for 18yo male with medulloblastoma 15 years post-diagnosis. The patient's IQ scores are low (Verbal IQ = 63, Performance IQ = 68, Full scale IQ = 63). * indicates an abnormal lipid peak at 1.6 ppm.

Figure 4. Relationships between lipid peak and IQ scores

Box plots showing Verbal IQ and Full Scale IQ scores for those with and without the abnormal lipid peak. Solid white lines within shaded boxes indicate the medians. Upper and lower quartiles are the top and bottom edges of the boxes, and fences go ± 1.5 times the interquartile range. Outliers are denoted outside the fences by solid black lines. Differences between Full Scale IQ and Verbal IQ scores for patients with or without a lipid peak were statistically significant ($p = 0.012$ and $p = 0.004$, respectively).

Table 1

Neuropsychological tests and results

Domain	Test Scores	n	Mean (SD) **	Range
General Intelligence	Full Scale IQ * [Wechsler Preschool & Primary Intelligence Scale Revised (WPPSI-R) [41] or Wechsler Abbreviated Scale of Intelligence (WASI) [27]]	31	91.2 (21.2)	46.0 – 138.0
Language	Verbal IQ * [WPPSI-R or WASI]	30	92.5 (21.2)	52.0 – 141.0
Visual - Perceptual	Performance IQ * [WPPSI-R or WASI]	29	91.7 (21.1)	50.0 – 127.0
Memory				
Total	Global Verbal Memory T-score [†] [California Verbal Learning Test Children or II (CVLT) [10,11]]	23	43.4 (14.0)	20.0 – 65.0
Delayed	Long Delay Free Recall z-score [‡] [CVLT]	23	−0.8 (1.5)	−4.0 – 1.5
Immediate	Digit Span scaled score [§] [McCarthy Scales [20], Wechsler Intelligence Scale for Children (WISC-III) [40] or Wechsler Adult Intelligence Scale (WAIS-III) [39]]	27	8.3 (3.7)	1.0 – 15.0
Executive Function	Trailmaking Test Part B z-score ^{‡,} [30]	19	1.8 (2.7)	−1.3 – 8.4
Processing Speed	Processing Speed Index standard score * [WISC-III or WAIS-III]	21	92.8 (25.2)	50.0 – 137.0
Academic				
Reading	Reading standard score * [Wide Range Achievement Test (WRAT-3) [38]]	23	88.9 (21.6)	44.0 – 121.0
Arithmetic	Arithmetic standard score * [WRAT-3]	23	88.3 (22.4)	44.0 – 131.0

* IQ/standard scores (mean = 100, SD = 15)

[†] t-scores (mean = 50, SD = 10)

[‡] z-scores (mean = 0, SD = 1)

[§] scaled scores (mean = 10, SD = 3)

^{||} On this test, a higher score indicates slower/poorer performance.

** SD = standard deviation

Table 2

¹H-MRSI data for ROIs

ROI	L/R*	Spectra (n)	Cho/NAA Mean (SD) [†]	Range	NAA/Cr Mean (SD) [†]	Range	Cho/Cr Mean (SD) [†]	Range
FGM	L	29	0.38 (0.11)	0.08 – 0.50	3.31 (1.04)	2.00 – 6.00	1.17 (0.32)	0.50 – 2.00
	R	25	0.39 (0.14)	0.07 – 0.63	3.61 (2.45)	2.00 – 14.0	1.20 (0.33)	0.50 – 2.00
FWM	L	25	0.45 (0.12)	0.17 – 0.66	3.42 (0.99)	2.28 – 6.00	1.48 (0.36)	0.50 – 2.00
	R	25	0.41 (0.13)	0.07 – 0.63	3.46 (1.11)	2.00 – 7.00	1.32 (0.38)	0.50 – 2.00
OPWM	L	29	0.46 (0.13)	0.08 – 0.80	3.06 (1.02)	1.25 – 6.50	1.35 (0.46)	0.50 – 3.00
	R	26	0.43 (0.14)	0.11 – 0.67	3.12 (1.34)	1.67 – 9.00	1.26 (0.34)	0.50 – 2.00
THAL	L	17	0.55 (0.18)	0.33 – 1.14	2.63 (0.37)	1.75 – 3.00	1.39 (0.30)	1.00 – 2.00
	R	18	0.54 (0.13)	0.27 – 0.89	2.65 (0.50)	1.67 – 3.67	1.39 (0.23)	1.00 – 1.68
PUT	L	19	0.51 (0.14)	0.18 – 0.75	2.47 (0.81)	1.92 – 5.50	1.18 (0.22)	0.80 – 1.50
	R	23	0.49 (0.14)	0.11 – 0.75	2.42 (0.70)	1.67 – 4.00	1.12 (0.30)	0.50 – 1.50
GP	L	18	0.53 (0.20)	0.10 – 0.80	2.44 (0.83)	1.50 – 5.00	1.16 (0.34)	0.50 – 2.00
	R	19	0.46 (0.12)	0.27 – 0.75	2.70 (0.80)	2.00 – 5.00	1.19 (0.31)	0.75 – 2.00
HIPP	L	15	0.75 (0.13)	1.00 – 0.57	1.93(0.40)	2.88 – 1.33	1.44 (0.35)	2.28 – 1.00
	R	16	0.67 (0.18)	1.00 – 0.33	1.95 (0.46)	3.00 – 1.33	1.28 (0.42)	2.00 – 0.67

Note: Caudate head excluded from analysis.

FGM = frontal grey matter, FWM = frontal white matter, OPWM = occipital parietal white matter, THAL = thalamus, PUT = putamen, GP = globus pallidus, HIPP = hippocampus

* L = left, R = right.

[†]SD = standard deviation.

Table 3

Correlations ($p \leq 0.05$)

Comparisons of Metabolite Ratios and NP Test Scores		n	Ratio	r	p value
NP Test	ROI				
Full Scale IQ	Left GP	18	Cho/Cr	-0.62	0.011
	Left PUT	19	Cho/NAA	-0.48	0.043
Verbal IQ	Left GP	18	Cho/Cr	-0.61	0.014
Performance IQ	Left GP	18	Cho/Cr	-0.57	0.024
Reading	Left PUT	19	NAA/Cr	0.59	0.034
Arithmetic	Left GP	18	Cho/Cr	-0.51	0.050