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Original Article

Magnetic Resonance Spectroscopy at Term-Equivalent Age in Extremely Preterm Infants: Association With Cognitive and Language Development

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ABSTRACT

BACKGROUND: Proton magnetic resonance spectroscopy can be used to assess brain integrity and maturation with age. **OBJECTIVE:** To compare regional cerebral magnetic resonance spectroscopy metabolite ratios in extremely low birth weight and healthy term control infants measured at term-equivalent age and to evaluate association between magnetic resonance spectroscopy metabolites and cognitive and language development at 18-22 months' corrected age. **METHODS:** Single-voxel point-resolved spectroscopy sequence was performed in a prospective cohort of 43 infants. Magnetic resonance spectroscopy metabolite ratios of *N*-acetylaspartate to choline-containing compounds and *N*-acetylaspartate to myo-inositiol in the hippocampus, cortex, and subventricular zone were associated with Bayley mental, cognitive, and language scores at 18-22 months' corrected age. **RESULTS:** The mean (±S.D.) gestation of the 31 extremely low birth weight population was 25 (±1.1) weeks and mean (±S.D.) birth weight was 749 (±133.9) g. Compared with healthy term control infants, extremely low birth weight infants exhibited consistently lower *N*-acetylaspartate-to-choline-containing compounds ratios in our three regions of interest, with differences reaching statistical significance for the subventricular zone and cortex regions. In multiple linear regression analyses, *N*-acetylaspartate-to-choline-containing compounds ratio in the subventricular zone, *N*-acetylaspartate-to-choline-containing compounds ratio in the cortex, and *N*-acetylaspartate-to-myo-inositiol ratio in the subventricular zone were significantly associated with Bayley mental scores at 18-22 months' corrected age. **CONCLUSIONS:** Magnetic resonance spectroscopy metabolite abnormalities at term-equivalent age appear to be significantly associated with cognitive and language development in extremely low birth weight infants.

Keywords: proton magnetic resonance spectroscopy (MRS), extremely preterm infants, extremely low birth weight (ELBW) infants, neurodevelopmental outcome

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Introduction

Up to 29% to 40% of extremely preterm survivors develop cognitive and language impairments.[1-4] Yet we currently lack accurate prognostic markers for early risk stratification. It is currently not possible to accurately diagnose cognitive and language impairments until early childhood.[5] Early identification of high-risk infants at term-equivalent age can

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reap immediate benefits through aggressive administration of early intervention services.[6] Cranial ultrasound exhibits poor sensitivity for detecting diffuse white matter abnormalities[7,8] and predicting neurodevelopmental impairments (NDI).[9] Although conventional magnetic resonance imaging (MRI) is better at detecting diffuse white matter abnormalities, it remains subjective and inaccurate at predicting cognitive impairments.[10] Quantitative MRI techniques, such as diffusion tensor imaging and proton magnetic resonance spectroscopy (MRS), offer an objective measure of cerebral microstructure and in vivo biochemistry, respectively.[11-15]

In MRS, different metabolites have characteristic resonant frequencies that allow their identification for quantification.[16] Tissue metabolic changes likely precede macrostructural and functional changes that can be detected soon after injury or abnormal development with a high degree of specificity. Therefore tissue metabolites may serve as important early diagnostic and prognostic biomarkers. In a recent meta-analysis of MRI studies in term infants with hypoxic-ischemic encephalopathy (HIE), MRS metabolite ratios exhibited the highest accuracy in predicting neurodevelopmental outcomes.[17] However, not much is known about the ability of MRS biomarkers to predict NDI in extremely preterm infants. Our goal was to compare regional cerebral MRS metabolite ratios in extremely low birth weight (ELBW; birth weight $\leq$1000 g) and healthy term control infants measured at term-equivalent age (term) and to evaluate the association of MRS metabolites at term-equivalent age with cognitive and language development at 18-22 months' corrected age.

Methods

Patient population

All ELBW infants from the Children's Memorial Hermann Hospital Neonatal Intensive Care Unit who survived to $\geq$34 weeks' postmenstrual age were eligible for the study. All healthy term newborns $\geq$37 weeks' gestation and with weight appropriate for gestation from the well-baby nursery were also eligible. Enrolled infants underwent MRI at 38 weeks' postmenstrual age or before discharge, if discharge occurred earlier. ELBW infants were enrolled between January 2008 and July 2009 and term infants between July 2008 and January 2010. ELBW infants with known congenital central nervous system anomalies, chromosomal anomaly, or high mechanical ventilatory support (mean airway pressure >15 and supplemental oxygen >50%) at the time of enrollment were excluded. The exclusion criteria for the term group were gestation $\geq$42 weeks, any congenital or chromosomal anomaly, multiple gestation pregnancy, maternal medical or pregnancy conditions, predelivery hospital admission, intrauterine exposures (drugs of abuse, cigarettes, alcohol, and medications with known or suspected neurological effects [steroids]), high forceps or vacuum delivery, perinatal distress or complications, neonatal intensive care unit admission, abnormal neurological examination, or suspected or known infection at birth. The hospital and University Institutional Review Board approved the study, and written informed consent was obtained from each infant's parent or guardian before enrollment.

Image acquisition and processing

Before the initiation of MRI scans, all infants were fed and swaddled. Med-Vac infant vacuum splint (CFI Medical Solutions, Fenton, MI), Insta-Putty Silicone Earplugs (E.A.R. Inc, Boulder, CO), and Natus MiniMuffs (Natus Medical Inc, San Carlos, CA) were used for restraint and noise reduction. No sedation was given to any subject. All scans were supervised by an experienced neonatologist, a neonatal transport nurse, and a neonatal research nurse.

Brain proton MRS was performed on a 3-T MRI scanner (Achieva; Philips Medical Systems, Best, the Netherlands) equipped with a 32-channel receiver system. An 8-channel phased-array head coil (Philips Medical Systems) was used for data acquisition. MRS data were acquired using a single-voxel point-resolved spectroscopy sequence from a voxel that was predominantly located in subventricular zone (SVZ), hippocampus (Hip), and frontal cortex (Cortex) areas (all in the right hemisphere; Fig 1). The MRS voxel size was 18 $\times$ 10 $\times$ 10 mm^3. These three regions were selected because they represent vulnerable regions in the preterm brain and for assessing the presence of neural progenitor cells in these regions[18] as part of a secondary project. The acquisition parameters were repetition time = 2000 ms, echo time = 35 ms, spectral width = 2000 Hz, 1024 data points, and 128 averages. Total acquisition time for each region was about 5 minutes. Axial, coronal, and sagittal images were acquired to position the MRS voxel location and regional saturation technique bands. To guarantee consistent quality MRS data and data acquisition at the precise locations with the same acquisition parameters, the same neonatologist, MRI physicist, and technologist were involved in all data collection.

The well-developed linear combination model-fitting procedure (LCModel; Steven Provencher Inc, Oakville, Ontario, Canada, version 6.2-1)[19] was used for quantitative analysis of the MRS data. This software automatically identifies and quantifies relative values of several well-characterized metabolites, including *N*-acetylaspartate (NAA) at 2.02 ppm, phosphocreatine and/or creatine (Cr) at 3.02 ppm, choline-containing compounds (Cho) at 3.22 ppm, and myo-inositiol (mI) at 3.56 ppm. Figure 2 is a representative MRS spectrum output for a study subject depicting the metabolic profile in the SVZ and analyzed using LCModel. We identified three cerebral metabolite ratios, NAA to Cr, Cho to Cr, and mI to Cr, in our three areas of interest, SVZ, Hip, and Cortex. Based on prior research[17,20] and to limit multiple comparisons, we only chose NAA-to-Cho and NAA-to-mI ratios as our main biomarkers of interest. Any estimated ratio with >20% S.D. (Cramer-Rao lower bounds) was considered to be unreliable and deleted from the data analysis.[19] All analyses were blinded to clinical variables, cranial ultrasound, and anatomic MRI findings. All conventional MRI scans were read by a neuroradiologist, which included using standardized assessment or definitions of white and gray matter maturation, signal abnormalities (e.g., hemorrhage, leukomalacia), and white matter diffuse excessive high signal intensity abnormalities.

Neurodevelopmental follow-up and assessment

Study infants were monitored at 18-22 months' corrected age in the High Risk Follow-up Clinic at the University of Texas Health Science Center at Houston. At the time of the follow-up visit, all patients underwent a complete neuromotor examination to assess gross motor function and ascertain presence of cerebral palsy by standardized National Institute of Child Health and Human Development Neonatal Research Network examiners. Additionally, a masked and certified examiner administered the cognitive and language subtests of the Bayley Scales of Infant and Toddler Development–III.[21]

Our primary outcome of interest—an individual infant's average of the Bayley-III cognitive and language scores—was labeled the mental score. This composite score approximates the content of the Bayley II Mental Developmental Index score[22] and was chosen because it permits a single primary outcome and facilitates comparison to studies using the second edition of the Bayley Scales test. Individual cognitive and language scores on the Bayley-III were evaluated independently as secondary outcomes.

Statistical analysis

Stata/IC 12 (StataCorp, College Station, TX) was used for all data analyses. Maternal, perinatal, and neonatal detailed history and data were prospectively collected for all enrolled ELBW infants during their neonatal intensive care unit stay. At the time of follow-up, additional