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Original article

Temporal brain metabolite changes in preterm infants with normal development

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Abstract

Objective: Preterm infants are at high risk for developmental delay, epilepsy, and autism spectrum disorders. Some reports have described associations between these conditions and gamma-aminobutyric acid (GABA) dysfunction; however, no study has evaluated temporal changes in GABA in preterm infants. Therefore, we assessed temporal changes in brain metabolites including GABA using single-voxel 3-Tesla (T) proton magnetic resonance spectroscopy (^{1}H-MRS) in preterm infants with normal development.

Methods: We performed 3T ^{1}H-MRS at 37–46 postmenstrual weeks (PMWs, period A) and 64–73 PMWs (period B). GABA was assessed with the MEGA-PRESS method. *N*-acetyl aspartate (NAA), glutamate–glutamine complex (Glx), creatine (Cr), choline (Cho), and myo-inositol (Ins) were assessed with the PRESS method. Metabolite concentrations were automatically calculated using LCModel.

Results: Data were collected from 20 preterm infants for periods A and B (medians [ranges], 30 [24–34] gestational weeks, 1281 [486–2030] g birth weight). GABA/Cr ratio decreased significantly in period B ($p = 0.03$), but there was no significant difference in GABA/Cho ratios ($p = 0.58$) between the two periods. In period B, NAA/Cr, Glx/Cr, NAA/Cho, and Glx/Cho ratios were significantly increased ($p < 0.01$), whereas Cho/Cr, Ins/Cr, and Ins/Cho ratios were significantly decreased ($p < 0.01$). There was no significant difference for GABA or Cho concentrations ($p = 0.52$, $p = 0.22$, respectively). NAA, Glx, and Cr concentrations were significantly increased ($p < 0.01$), whereas Ins was significantly decreased ($p < 0.01$).

Conclusions: Our results provide new information on normative values of brain metabolites in preterm infants.

Keywords: Brain metabolites; Magnetic resonance spectroscopy; Preterm infants

1. Introduction

Recent clinical advances in perinatal care have increased the survival rate of preterm infants. However, preterm infants still have higher risks of cerebral palsy, cognitive deficiency, behavioral or psychological

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problems, blindness, hearing loss, epilepsy, and autism spectrum disorders [1,2]. Diagnoses of intraventricular hemorrhage or periventricular leukomalacia made using cranial ultrasonography (US) or conventional magnetic resonance imaging (MRI) show sufficient sensitivity to detect delayed complications such as spastic diplegia or quadriparesis and are usually the first imaging modalities used in preterm infants [3]. However, they cannot completely exclude later adverse neurologic outcomes: for example, preterm infants can appear normal on neonatal US and exhibit no white matter lesions on MRI but later develop cerebral palsy and suffer cognitive delays.

Proton magnetic resonance spectroscopy (^{1}H-MRS) can noninvasively measure various brain metabolites that are known to be altered during rapid brain development in the first year of life [4]. MRS may provide additional diagnostic value to cranial US and MRI in infants. The use of 3 Tesla (T) MRS offers better quality spectra in shorter acquisition times than 1.5T MRS, and 3T MRS can also discriminate gamma-aminobutyric acid (GABA) spectrum. An immunohistochemical study showed GABAergic neuron loss following perinatal brain injury and revealed that white matter lesions affect cortical development and GABA receptor expression in cortical layers; the authors suggested that this may contribute to the pathogenesis of neurologic deficits [5]. GABA abnormalities have also been reported in the settings of childhood autism spectrum disorders and epilepsy [6,7].

The purpose of this study was to assess temporal changes in brain metabolites including GABA with single-voxel 3T ^{1}H-MRS in preterm infants with normal development until 64–73 postmenstrual weeks (PMWs, the gestational weeks plus the weeks after birth).

2. Materials and methods

2.1. Patients

From April 2014 to March 2015, we prospectively recruited 79 preterm infants (gestational age $\leqslant$ 34 weeks) who were admitted to our neonatal intensive care unit. Cranial US, conventional MRI, and ^{1}H-MRS were performed at 37–46 PMWs (period A). Follow-up MRI and ^{1}H-MRS scans were performed at 64–73 PMWs (period B). The analysis included infants with data for both periods who were determined to have normal development at period B. Of 79 preterm infants, we excluded 59 due to early death ($n = 2$), major anomaly ($n = 1$), respiratory failure ($n = 1$), clip ligation of patent ductus arteriosus ($n = 6$), hospital transfer before examination ($n = 14$), no written informed consent ($n = 6$), acute disease ($n = 16$), motion artifacts ($n = 4$), technical problems with ^{1}H-MRS ($n = 6$), and MRI abnormalities and/or developmental delay at period B ($n = 3$). We ultimately included 20 preterm infants in the analysis.

The developmental quotient (DQ) was assessed using the Enjoji Scale of Infant Analytical Development in period B. A DQ score <70 indicated developmental delay [8]. The Denver Development Screening Test II adopted for Japanese children (DDST II) was also administered. Failure of $\geqslant$2 items out of 28 total items indicated abnormal development [9].

This study was approved by the ethics committee of Iwate Medical University (approval number H24-37).

2.2. MRS examination

^{1}H-MRS examinations were conducted using a 3T scanner (Discovery MR750 3.0T DV24.0, GE Healthcare, Milwaukee, WI, USA) equipped with an eight-channel head coil. All subjects were sedated with oral triclofos sodium (80 mg/kg) 30 min before the examination. Heart rate and transcutaneous oxygen saturation were monitored during examinations. Single-voxel ^{1}H-MRS was performed on the volume of interest (VOI), a $25 \times 25 \times 25$ mm volume in the right basal ganglia (BG) on the axial section through the BG under the guidance of T2-weighted images (Fig. 1). Since the VOI was larger than that in our previous report using a 1.5T multivoxel MRS [10], the frontal lobe was not acquired in this study. GABA was assessed with the Meschier-Garwood point-resolved echo spectroscopy (MEGA-PRESS) method. We used the difference-editing technique for optional measurement of GABA. *N*-acetyl aspartate (NAA), glutamate–glutamine complex (Glx), creatine (Cr), choline (Cho), and myo-inositol (Ins) were assessed with the PRESS method. The acquisition parameters were as follows: reception time = 1500 ms, echo time = 68 ms, number of excitations = 256, and acquisition time = 6 min 54 s. High-order global shimming and optimization of radio frequency power for water suppression were automatically performed.

Brain metabolite concentrations in the BG were automatically calculated using LCModel version 6.1 (S-provencher Inc., Oakville, ON, Canada). Only results with a standard deviation $\leqslant$30% were included in the analysis, where the % standard deviation reflected the Cramer-Rao lower bound.

2.3. Statistical analyses

Wilcoxon signed-rank tests were used to compare temporal changes in brain metabolite ratios and raw brain metabolite concentrations between the two periods. Statistical analyses were performed using SPSS Ver. 22 (IBM Inc., Armonk, NY, USA). A *p*-value less than 0.05 was considered statistically significant.