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Normal lactate concentration range in the neonatal brain

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ABSTRACT

Objective: Lactate peaks are occasionally observed during *in vivo* magnetic resonance spectroscopy (MRS) scans of the neonatal brain, even in healthy patients. The purpose of this study was to investigate the normal range of neonatal brain lactate concentration, as a definitive normal range would be clinically valuable.
Methods: Using a clinical 3T scanner (echo/repetition times, 30/5000 ms), single-voxel MRS data were obtained from the basal ganglia (BG) and centrum semiovale (CS) in 48 healthy neonates (postconceptional age (PCA), 30–43 weeks), nine infants (age, 1–12 months old), and 20 children (age, 4–15 years). Lactate concentrations were calculated using an MRS signal quantification program, LCModel. Correlations between regional lactate concentration and PCA (neonates), or age (all subjects) were investigated.
Results: Absolute lactate concentrations of the BG and CS were as follows: neonates, 0.77 mM (0–2.02) [median (range)] and 0.77 (0–1.42), respectively; infants, 0.38 (0–0.79) and 0.49 (0.17–1.17); and children, 0.17 (0–0.76) and 0.22 (0–0.80). Overall, subjects' lactate concentrations decreased significantly with age (*Spearman*: BG, $n = 61$, $\rho = -0.38$, $p = 0.003$; CS, $n = 68$, $\rho = -0.57$, $p < 0.001$). However, during the neonatal period no correlations were detected between lactate concentration in either region and PCA.
Conclusion: We determined normal ranges of neonatal lactate concentration, which may prove useful for diagnostic purposes. Further studies regarding changes in brain lactate concentration during development would help clarify the reasons for higher concentrations observed during the neonatal period, and contribute to improvements in diagnoses.

1. Introduction

Lactate peaks are occasionally observed during *in vivo* magnetic resonance spectroscopy (MRS) in the neonatal brain, even in healthy individuals [1–7]. Therefore, clinically, it would be useful to know the normal range of brain lactate level in neonates to provide important information when diagnosing patients' conditions. However, it can be difficult to quantify lactate peaks associated with low lactate concentrations, and peaks that exhibit poor signal-to-noise ratios (SNR) or overlap with lipid/macromolecule peaks. In addition, clinical MRS data obtained in limited time is also difficult to quantify.

Previously, we reported neonatal brain concentrations of major metabolites (creatine and phosphorylcreatine (Cr), free choline and other choline-containing compounds (Cho), *N*-acetylaspartate and *N*-acetyl-aspartyl-glutamate (NAA), myo-inositol (mIns), and glutamate and glutamine complex (Glx)) [7]. To quantify the concentration of each metabolite, automatic quantification software, LCModel [8], was used because of its simplicity and minimal user-dependent bias. In LCModel, the reliability of data regarding metabolite concentrations and peak existence is indicated by percentage standard deviation (%SD) values, which are equivalent to Cramér-Rao lower bound values [9]. The criterion for reliability used in our previous study was a %SD of ≤30 [7]. When a metabolite displays a

Abbreviations: BG, basal ganglia; Cho, free choline and choline-containing compounds; Cr, creatine and phosphorylcreatine; CS, centrum semiovale; Glx, glutamate and glutamine complex; mIns, myo-inositol; MRS, magnetic resonance spectroscopy; NAA, *N*-acetylaspartate and *N*-acetyl-aspartyl-glutamate; PCA, postconceptional age; %SD, percentage standard deviation; SNR, signal-to-noise ratio; TE, echo time; TR, repetition time; VOI, volumes of interest.

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concentration of zero, its %SD value is infinite. Since a number of lactate peaks exhibited low concentrations and large %SD values, they had to be excluded from analysis. Therefore, it remains unclear what levels of lactate are normal in healthy neonates.

In the current study, for clinical assessment purposes, we used LCModel to investigate the normal range of neonatal brain lactate levels. While the potential subjects that underwent pre-screening prior to this study were the same as those examined in our previous study [7], we made several changes to the inclusion/exclusion criteria. For example, an additional screening step based on subjects' subsequent clinical health was added. In addition, stricter criteria were used instead of %SD values. Specifically, to assess reliability of the concentration data obtained using LCModel, the results were compared with data acquired using a traditional peak-area measurement method.

2. Materials and methods

2.1. Ethics statement

This study was approved by the Institutional Ethical Review Board of Kanagawa Children's Medical Center, where all clinical data used in this study were acquired. The review board waived written informed consent.

2.2. Subjects

In our children's medical center, routine MR examination (1.5 or 3T) of the brain also includes single-voxel MRS. Neonates undergo MR examination because of neurological symptoms such as hypoxic–ischemic encephalopathy, suspicion of organic disease, or as part of routine pre-discharge evaluations. From October 2009 to November 2012, 235 neonates with postconceptional ages (PCA) of 30–43 weeks underwent MRS using a 3T MR scanner. The population of 235 neonates were as follows: preterm birth before 32 weeks, 82; hypoxic–ischemic encephalopathy, 49; brain anomaly, 32; multiple anomaly, 20; small for gestational age, 8; twin-to-twin transfusion, 7; seizure, 7; congenital heart disease, 6; respiratory failure, 5; inborn error of metabolism, 4; hypoglycemia, 3; septic shock, 3; hypovolemic shock, 3; congenital cytomegalovirus infection, 3; congenital adrenal hyperplasia, 1; not doing well, 1; and jaundice, 1.

To obtain lactate level in the healthy neonatal brain, we excluded potential subjects at the first sign of any clinical abnormality, radiologically, and/or at follow-up examination. Other potential subjects who demonstrated psychomotor retardation, cerebral palsy, and/or hearing problems at follow-up examination, performed at a corrected age of 1.5 years, were also excluded. MR spectral qualities were also considered (see Section 2.3 *Proton MRS*). Consequently, 48 neonates were eventually selected. Since two neonates were examined twice in different weeks, the net number of neonates was 46. They included 33 preterm infants (14 males, 19 females; gestational age (GA), 23–36 weeks; studied at PCA of 31–42 weeks), and 13 term infants (5 males, 8 females; GA, 37–41 weeks; studied at PCA of 38–42 weeks). As controls, the MRS findings of nine infants (6 males, 3 females; age, 1–12 months; mean age ± standard deviation, 4.8 ± 4.6 months), and 20 children (11 males, 9 females; age, 4–15 years, mean age, 9.2 ± 3.4 years) were also investigated. No control subjects displayed clinically significant symptoms or radiological abnormalities. Subjects' clinical findings were evaluated both at the time of the initial scan and during follow-up examination by an experienced pediatric radiologist, board-certified neonatologists, and pediatric specialists.

2.3. Proton MRS

All MRS data were acquired using a clinical 3T MR scanner (Magnetom Verio; Siemens, Erlangen, Germany). Single-voxel MRS scans were acquired with a point-resolved spectroscopic localization sequence [10], involving an echo time (TE) of 30 ms, repetition time of 5000 ms, and excitation number of 6 to 32. The basal ganglia (BG), which are predominately gray matter, and the centrum semiovale (CS), which is predominately white matter were selected as the volumes of interest (VOI). The cerebrospinal region was excluded from the VOI. Sizes of VOI in the BG and CS were as follows: 2.4–6.7 and 3.6–7.3 mL, respectively, in neonates, 5.8–14.8 and 5.6–14.7 mL in infants, and 7.9–19.2 and 7.9–19.2 mL in children. To obtain H_2O proton peak data, the spectra of the same VOI were acquired without the H_2O presaturation pulse sequence. Approximately 5 min were needed to obtain the pairs of MRS scans (with/without H_2O presaturation) for each region, and the total time required to perform MRS examinations of the two regions was around 10 min. A detailed description of the protocol for MR examinations was provided in our previous study [7]. According to the above criteria, only data that exhibited SNR of ≥8 and unsuppressed H_2O proton peak, full width, at half-maximum values of ≤10 Hz were selected. The SNR was defined as the ratio of the spectrum maximum minus the baseline divided by twice the root-mean-square residual, as described previously [9].

As the lactate signal can contain lipid/macromolecule signals with the quantification methods used in this study, it was termed Lac+. For the quantitative values of Lac+, "concentration" was used as a convenient descriptor. Lac + signals were quantified using LCModel software (version 6.2-1G), and their concentrations were estimated using the water-scaling method, *i.e.*, based on the intensity of lactate and H_2O signals [9]. The water concentrations of the BG and CS were assumed to be 49.7 and 46.9 M, respectively, in neonates, 44.4 and 42.8 M in infants, and 41.7 and 37.8 M in children [5,11]. To assess the reliability of lactate output values of LCModel, they were compared with those obtained using a traditional manual peak-area measurement technique. Then, the peak-areas of lactate and Cr were manually fitted using in-house software running on MATLAB (The MathWorks, Natick, MA, USA). Then, Lac + concentration was calculated using the following equation:

$$\text{Lac} + \text{conc.} = \frac{\text{Lactate peak area} \,/\, 3 \text{ protons}}{\text{Cr peak area} \,/\, 3 \text{ protons}} \times \text{Cr conc.}^{LCM}, \quad (1)$$

where Cr conc.^{LCM} is the Cr concentration obtained using LCModel.

IBM SPSS Statistics 23 (SPSS, Chicago, IL, USA) was used for all statistical analyses. Correlations between lactate concentrations obtained using the two analytical methods (LCModel and the peak-area measurement method) were investigated using Pearson's correlation coefficient. Correlations between lactate concentration and PCA (or age) were investigated using Spearman's rank correlation coefficient. Comparison of lactate concentrations of the BG and CS in neonates was performed using Mann–Whitney U tests. *P*-values < .05 were considered statistically significant.

3. Results

In this study, 82 MR spectra (41 BG and 41 CS) for 48 neonates (out of 235 pre-screened neonates) were included in analyses. All MRS spectra exhibited clear peaks for the five major brain metabolites (Cr, Cho, NAA, mIns, and Glx), and lactate doublet peaks were also frequently observed in neonates, as shown in Fig. 1.