OBSTETRICS

Brain metabolite alterations in infants born preterm with intrauterine growth restriction: association with structural changes and neurodevelopmental outcome

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BACKGROUND: Intrauterine growth restriction and premature birth represent 2 independent problems that may occur simultaneously and contribute to impaired neurodevelopment.

OBJECTIVE: The objective of the study was to assess changes in the frontal lobe metabolic profiles of 1 year old intrauterine growth restriction infants born prematurely and adequate-for-gestational-age controls, both premature and term adequate for gestational age and their association with brain structural and biophysical parameters and neurodevelopmental outcome at 2 years.

STUDY DESIGN: A total of 26 prematurely born intrauterine growth restriction infants (birthweight <10th centile for gestational age), 22 prematurely born but adequate for gestational age controls, and 26 term adequate-for-gestational-age infants underwent brain magnetic resonance imaging and magnetic resonance spectroscopy at 1 year of age during natural sleep, on a 3 Tesla scanner. All brain T1-weighted and diffusion-weighted images were acquired along with short echo time single-voxel proton spectra from the frontal lobe. Magnetic resonance imaging/magnetic resonance spectroscopy data were processed to derive structural, biophysical, and metabolic information, respectively. Neurodevelopment was evaluated at 2 years of age using the Bayley Scales 3rd edition, assessing cognitive, language, motor, socioemotional, and adaptive behavior.

RESULTS: Prematurely born intrauterine growth restriction infants had slightly smaller brain volumes and increased frontal lobe white matter mean diffusivity compared with both prematurely born but adequate for gestational age and term adequate for gestational age controls. Frontal lobe N-acetylaspartate levels were significantly lower in prematurely born intrauterine growth restriction than in prematurely born but adequate for gestational age infants but increased in prematurely born but adequate for gestational age compared with term adequate-for-gestational-age infants. The prematurely born intrauterine growth restriction group also showed slightly lower choline compounds, borderline decrements of estimated glutathione levels, and increased myoinositol to choline ratios, compared with prematurely born but adequate for gestational age controls. These specific metabolite changes were locally correlated to lower gray matter content and increased mean diffusivity and reduced white matter fraction and fractional anisotropy. Prematurely born intrauterine growth restriction infants also showed a tendency for poorer neurodevelopmental outcome at 2 years, associated with lower levels of frontal lobe N-acetylaspartate at 1 year within the preterm subset.

CONCLUSIONS: Preterm intrauterine growth restriction infants showed altered brain metabolite profiles during a critical stage of brain maturation, which correlate with brain structural and biophysical parameters and neurodevelopmental outcome. Our results suggest altered neurodevelopmental trajectories in preterm intrauterine growth restriction and adequate-for-gestational-age infants, compared with term adequate-for-gestational-age infants, which require further characterization.

Key words: brain metabolism, brain structure, intrauterine growth restriction, magnetic resonance spectroscopy, neurodevelopment, preterm birth

Intrauterine growth restriction (IUGR) caused by placental insufficiency affects 5−10% of all pregnancies. This condition is associated with fetal undernutrition and chronic hypoxia[1,2] and has 2 distinct clinical presentations: early- and late-onset IUGR. Whereas the late-onset subtype represents a milder but more prevalent form of IUGR,[3,4] early-onset IUGR is a severe condition, associated with fetal deterioration and elective preterm delivery.[5]

From a brain structural perspective, late-onset IUGR fetuses present differences in cortical development,[6] corpus callosum,[7] brainstem, and cerebellum.[8] With regard to brain metabolism, reduced levels of N-acetyl aspartate (NAA; a neuronal marker) ratios to choline compounds (Cho; maker of cell membrane turnover [NAA/Cho]) or creatine (Cr; implicated in cellular energetics [NAA/Cr]) have been detected in fetuses with early-[9,10] and late-onset IUGR.[9,10] Moreover, an association between brain microstructural changes (smaller corpus callosum) and altered metabolic profile (lower NAA/Cho) has been shown in late-IUGR fetuses.[11] These prenatal brain developmental changes reflect the so-called fetal brain programming under placental insufficiency.

Regardless of its clinical presentation, IUGR is associated with suboptimal neurodevelopmental outcome,[12-17] mostly affecting frontal networking functions such as attention, creativity, language, memory performance, and learning abilities.[13] Efforts have been made to unveil which mechanisms are involved in brain remodeling under IUGR conditions. However, it is difficult to address the differential effects of early-onset IUGR and premature birth because they represent 2 independent conditions occurring simultaneously,

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and both can contribute to an impaired neurodevelopment.[18]

Understanding the specific contribution of early-onset IUGR to this problem could be paramount for improving its clinical management and foster discussion about potential perinatal interventions. The first year of life represents a very active period of brain maturation[19] and is therefore suitable for such assessment.

Previous studies on early-onset IUGR have reported reduced brain volumes and altered cortical development during the neonatal period[20,21] and altered white matter (WM) microstructure[22] and global gray matter (GM) decrements at 1 year of age.[22,23] Moreover, a mixed population of 1 year old early/late-IUGR infants showed structural brain networks with a reduced level of organization[24,25] and specific correlations between brain regional circuit metrics and related neurodevelopmental outcomes.[26]

Although 1 year old late-onset IUGR infants have shown increased frontal lobe levels of NAA/Cr,[27] brain metabolic profile changes in the early-onset form have not yet been assessed at this age. Therefore, it remains unclear whether neurodevelopmental changes in early- and late-onset IUGR are underlied by similar metabolic alterations.

The purpose of this study was to assess changes in brain metabolite profiles of 1 year old preterm infants with early-onset IUGR (P-IUGR) as compared with adequate-for-gestational-age controls, both premature (P-AGA) and born at term (T-AGA), and their regional association with brain structural and biophysical parameters, and neurodevelopmental outcome at 2 years.

Materials and Methods

Study cohort

This study is part of a larger prospective research program on IUGR involving fetal and short- and long-term postnatal follow-up. The protocol used was approved by the local institutional ethics committee (review board 2010/5736), and all parents gave their written informed consent.

A consecutive sample of 74 neonates was prospectively recruited at birth. Subjects were classified according to their gestational age (GA) at birth and birthweight centile, corrected for sex and GA at birth[28]; GAs were established from fetal crown-rump lengths in the first trimester.[29] This sample included a group of 26 singleton neonates delivered after 37 weeks, with birthweight above the 10th centile (T-AGA); and 48 neonates delivered before 37 weeks (preterm), including 60% singleton pregnancies.

Preterm subjects with a birthweight above the 10th centile were classified as P-AGA (n = 22) and those below the 10th centile as P-IUGR (n = 26). Infants with congenital malformations, chromosomal abnormalities, infections, or chronic maternal pathology were not eligible for this study.

Magnetic resonance (MR) acquisition

Brain magnetic resonance imaging (MRI) was carried out at 16.1 (±2.4) months of age, without sedation, during natural sleep. Data were acquired with a 3.0 T scanner (TIM TRIO; Siemens Diagnostics Healthcare, Erlangen, Germany), and a head matrix radiofrequency coil was used. The total length of each MR examination did not exceed 45 minutes.

High-resolution, T1-weighted anatomical images were acquired with magnetization prepared rapid acquisition gradient echo: repetition time (TR), 2050 milliseconds; echo time (TE), 2.41 milliseconds; inversion time, 1050 milliseconds; 192 sagittal slices with 0.9 mm thickness, without interslice gap; in-plane acquisition matrix, 256 × 256; field of view, 220 × 220 mm; and voxel size, 0.86 × 0.86 × 0.9 mm.

Proton spectra were then obtained from the frontal lobe region using single-voxel point resolved spectroscopy (PRESS): voxel size, 40 × 20 × 20 cubic millimeters; TR, 2000 milliseconds; TE, 30 milliseconds; transients, 98; water suppression module, chemical shift selective; acquisition time, 3.5 minutes. A reference spectrum was also acquired, with 16 transients and no water suppression.

Diffusion-weighted images were also acquired using single-shot, echo-planar imaging: TR, 9300 milliseconds; TE, 94 milliseconds; 40 axial slices, 3 millimeter thickness, without interslice gap; matrix, 122 × 122; field of view, 200 × 200 millimeters, voxel size, 1.64 × 1.64 × 3 millimeters; 30 diffusion directions (b = 1000 s/mm^2), and a baseline image (b = 0 s/mm^2). Structural MR images were reviewed for the presence of anatomical abnormalities by an experienced neuroradiologist blinded to the group membership.

Postprocessing of MRI and magnetic resonance spectroscopy (MRS) data

The T1-weighted and diffusion-weighted images were used for brain segmentation (Figure 1), computing structural and biophysical regional parameters, such as WM, GM, cerebrospinal fluid (CSF), average fractional anisotropy (FA) and mean diffusivity (MD), integrity,[30] and directionality[31] of the fiber tracts. This is detailed in Supplemental Methods 1. All acquired MRI structural and diffusion images were visually inspected for apparent or aberrant artifacts and subjects excluded accordingly.

MRS data were quantified using linear combination model fitting (LC model, Figure 2),[32] as detailed in Supplemental Methods 2. MRS data were selected for further analysis only if the following applied: no gross visual artifacts were detectable and the spectral pattern was interpretable[33]; signal-to-noise ratio >10; and estimated full width at half maximum <0.1 parts per million. The data were quantified based on the reference water scans, and the metabolite ratios to total Cr and to the total Cho were determined. The brain metabolites were assigned according to the literature.[34]

Neurodevelopmental assessment

Neurodevelopmental outcome was assessed at 22.5 (±2.5) months of age, using the Bayley Scales of Infant and Toddler Development test, third edition (BSID-III).[35,36] Five distinct areas were evaluated: cognitive, language, motor,