OBSTETRICS

Brain metabolite differences in one-year-old infants born small at term and association with neurodevelopmental outcome

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OBJECTIVE: We assessed brain metabolite levels by magnetic resonance spectroscopy (MRS) in 1-year-old infants born small at term, as compared with infants born appropriate for gestational age (AGA), and their association with neurodevelopment at 2 years of age.

STUDY DESIGN: A total of 40 infants born small (birthweight <10th centile for gestational age) and 30 AGA infants underwent brain MRS at age 1 year on a 3-T scanner. Small-born infants were subclassified as late intrauterine growth restriction or as small for gestational age, based on the presence or absence of prenatal Doppler and birthweight predictors of an adverse perinatal outcome, respectively. Single-voxel proton magnetic resonance spectroscopy (^{1}H-MRS) data were acquired from the frontal lobe at short echo time. Neurodevelopment was evaluated at 2 years of age using the Bayley Scales of Infant and Toddler Development, Third Edition, assessing cognitive, language, motor, social-emotional, and adaptive behavior scales.

RESULTS: As compared with AGA controls, infants born small showed significantly higher levels of glutamate and total N-acetylaspartate (NAAt) to creatine (Cr) ratio at age 1 year, and lower Bayley Scales of Infant and Toddler Development, Third Edition scores at 2 years. The subgroup with late intrauterine growth restriction further showed lower estimated glutathione levels at age 1 year. Significant correlations were observed for estimated glutathione levels with adaptive scores, and for myo-inositol with language scores. Significant associations were also noticed for NAA/Cr with cognitive scores, and for glutamate/Cr with motor scores.

CONCLUSION: Infants born small show brain metabolite differences at 1 year of age, which are correlated with later neurodevelopment. These results support further research on MRS to develop imaging biomarkers of abnormal neurodevelopment.

Key words: brain metabolism, intrauterine growth restriction, magnetic resonance spectroscopy, small for gestational age

Cite this article as: Simões RV, Cruz-Lemini M, Bargalló N, et al. Brain metabolite differences in one-year-old infants born small at term and association with neurodevelopmental outcome. Am J Obstet Gynecol 2015;213:210.e1-11.

Small-born infants are those with a birthweight <10th centile for gestational age. This represents a common condition affecting up to 10% of all deliveries at term[1] and is associated with a higher risk for adverse neurological and cardiovascular outcome.[2] During gestation, fetal smallness is identified by ultrasound as an estimated fetal weight <10th centile for gestational age, and a thorough Doppler ultrasound assessment is necessary in such cases to evaluate the severity. Among the late-onset forms of fetal smallness, about two thirds present signs of severity, including prenatal Doppler cerebroplacental ratio (middle cerebral to umbilical artery pulsatility index ratio <5th centile and/or mean uterine artery pulsatility index >95th centile and/or estimated fetal weight <3rd centile), and are associated with poorer perinatal outcome.[3-5] It has been suggested that these cases represent true forms of placental insufficiency and should be considered as late-onset intrauterine growth restriction (IUGR).[6] The remaining one-third of

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Received Oct. 29, 2014; revised Feb. 6, 2015; accepted April 14, 2015.

This work was funded by grants from the Cerebra Foundation for the Brain Injured Child, Carmarthen, Wales, United Kingdom; Obra Social "La Caixa" and Fundación Dexeus, Barcelona, Spain; and Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR) 2014 Suport a Grups de Recerca (SGR) grant number 928. M.S.-C. was supported by a Rio Hortega postdoctoral fellowship, Spain (CM10/00222).

The authors report no conflict of interest.

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0002-9378/$36.00 • http://dx.doi.org/10.1016/j.ajog.2015.04.011

cases of late-onset fetal smallness, without signs of severity, should be considered as small for gestational age (SGA).[7] While SGA fetuses have been commonly defined as constitutionally small, there is no solid evidence to support this and they may represent another form of pathological smallness. Regardless of the clinical presentation, both clinical groups of small fetuses are associated with poorer neurodevelopment as early as the neonatal period and during later stages,[8-12] affecting mostly functions associated with frontal networking such as attention, creativity, language, memory performance, and learning abilities.[8] The neurostructural and neurofunctional phenotypes associated with fetal smallness, and their relationships, are still only partially understood.

The study of brain metabolism is an important tool to assess neurodevelopment, given their intrinsic relationship. Previous studies have shown that small fetuses have lower frontal lobe ratios of N-acetylaspartate (NAA, a neuronal marker) to choline compounds (Cho, marker of cell membrane turnover) and lower ratios of NAA to creatine (Cr, a potential glial marker implicated in cellular energetics).[13,14] These metabolic changes have been associated with disrupted brain maturation[13] but it remains unknown to what extent they are a reflection of the brain tissue exposure to an adverse in utero environment, and how they may underlie true neurostructural changes[15-20] leading to brain remodeling and future changes in neurodevelopmental function.

In this study we addressed the hypotheses that brain metabolite changes were present in the frontal lobe of 1-year-old small-born infants at term, and could be correlated with neurodevelopmental outcome at 2 years of age.

Materials and Methods

Study cohort and clinical perinatal data

This study is part of a larger prospective research program on growth restriction 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 participants gave their written informed consent. A consecutive sample of 70 neonates were prospectively recruited at birth, all delivered at term from singleton pregnancies and presenting normal umbilical artery pulsatility index (<95th centile) at the time of delivery.[21-23] Subjects were classified as appropriate for gestational age (AGA) (30 subjects) or small (40 subjects), based on their birthweight above or below the 10th centile,[24] respectively. In all cases, gestational age was corrected from fetal crown-rump length in the first trimester.[25] Additionally, the small-born neonate group was subclassified according to recent criteria proposed,[7] considering their birthweight and prenatal ultrasound Doppler parameters from the scan closest to the time of delivery. Thus, small-born infants were classified as late-onset IUGR (31 subjects) if signs of severity were present (cerebroplacental ratio <5th centile[26] and/or mean uterine artery pulsatility index >95th centile[26] and/or a birthweight <3rd centile[7]), or as SGA (9 subjects) when none of these factors were present. Middle cerebral, umbilical, and mean uterine artery pulsatility index parameters were measured as reported earlier,[3,26] using a Siemens Sonoline Antares (Siemens, Erlangen, Germany) system with a 6 to 2MHz linear curved-array transducer.

Neonates with congenital malformations, chromosomal abnormalities, infections, chronic maternal pathology, or noncephalic presentations were not eligible for this study. Maternal and perinatal data were prospectively recorded in most study patients.

Magnetic resonance acquisition

Brain magnetic resonance imaging was carried out at 14 (±1.5) 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 magnetic resonance examination did not exceed 45 minutes. Reference T1-weighted anatomical images were acquired with magnetization prepared rapid acquisition gradient echo. Single-voxel proton spectroscopy (^{1}H-MRS) was carried out with point-resolved spectroscopy from the frontal lobe region (Figure 1, A), using the following parameters: 40 × 20 × 20 mm^3 voxel size, 2000-millisecond repetition time, 30-millisecond echo time, 98 averages, chemical shift selective water suppression, and 3-minute 24-second acquisition time. A reference spectrum with 16 averages was also acquired, without water suppression. Finally, T2-weighted images (half-Fourier acquisition single-shot turbo spin-echo) were obtained; magnetic resonance spectroscopy (MRS) was repeated if artifacts were detected (eg, due to head movements). Structural magnetic resonance images were reviewed for the presence of anatomical abnormalities by an experienced neuroradiologist blinded to group membership.

MRS postprocessing

MRS data with gross visual artifacts and/or absence of an interpretable metabolic pattern[27] were directly discarded. The remaining MRS data were processed using linear combination model-fitting (LCModel; S. Provencher Inc., http://s-provencher.com/pages/lcmodel.shtml).[28] The basis sets used included a total of 23 metabolites: alanine, aspartate, Cr and phosphocreatine (total Cr), gamma aminobutyric acid, glucose, glutamine, glutamate, glycine, phosphocholine and glycerophosphocholine (choline compounds, Cho), glutathione, myo-inositol, lactate, N-acetylaspartate, and N-acetylaspartylglutamate (NAAG) (abbrieviated together as total NAA, NAAt), phosphoethanolamine, scyllo-inositol, taurine, threonine, valine, acetate, and ascorbate. Lipid and macromolecule contributions were also included in the modeling. All MRS data analyzed had an estimated signal-to-noise ratio >10 and only spectra with an estimated full width at half maximum <0.1 ppm were selected for further analysis. Those metabolite fittings with Cramér-Rao lower bounds (estimated SDs of the estimated concentration)[29] >50% were also discarded and only metabolite changes of at least twice their Cramér-Rao lower bounds (95% confidence interval) were selected, unless indicated otherwise. The data