Quantitative MR Demonstration of altered of Brain Development in Newborns following Intrauterine Growth Restriction

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Introduction

Placental insufficiency is a major pathology of human gestation and is associated with fetal intrauterine growth restriction (IUGR). Fetal IUGR is an important cause of perinatal mortality and morbidity (1,2) and is subsequently associated with significant neurodevelopmental disabilities in cognitive function, activity, self-regulation, language, abstract reasoning, recognition memory, concentration, attention, mood and temparement control and school performance, as shown in multiple follow-up studies of such infants. These studies have not revealed a neurostructural correlate, which could include abnormalities in brain development.

There is strong experimental evidence for a deleterious effect of early malnutrition on brain development. Animal studies clearly demonstrate the negative impact of chronic intrauterine hypoxia and protein restriction on cell number and cell size with overall lighter brain weight and lower DNA content as well as reduced synapse numbers (3,4). Altered composition of free fatty acids as observed in substrate deficient IUGR further affect brain lipid composition and myelination. Using 3-D volumetric MRI techniques, we studied the impact of IUGR on brain growth and brain tissue composition during early brain development in premature newborns with IUGR .

Methods

*Subjects:*Nine preterm (gestational age 28 to 33 weeks) infants were studied, at post menstrual ages (PMA = Gestational age + Postnatal Age) 39-40 weeks using an advanced quantitative volumetric 3D MRI technique to quantify cerebral tissue volumes and to assess the effects of IUGR (defined by symmetric growth below 10%ile) on brain development. Four infants with GA at birth (31.2±2.3 weeks) with birthweights <10%ile (1120g±430g) (IUGR) were compared with 5 infants with GA at birth (30.4±1.5 weeks) with birthweights (1480±320g). Infants studied were free of prematurity-associated cerebral pathology, such as intraventriuclar hemorrhage, ventriculomegaly or periventricular leukomalacia.

Procedure: For the MR studies the infants were positioned in a vacuum pillow in the scanner and monitored with ECG and pulse oximetry (Maglife, Bruker-Odam). Earmuffs (Natus Medical Inc. San Carlos, CA 94070) were used to minimize noise exposure. No sedation was used for any of the studies.

*Image Acquisition :*MRI scanning was performed using a 1.5 T Marconi MR system. For the acquisition of the primary MR data, two different imaging modes were applied: a 3 dimensional Fourier Transform fast gradient recalled sequence (1.5mm coronal slices, flip angle 45o;repetition time 35 msec; echo time 5 msec; field of view 18 cm; matrix 256x256) and a double echo (proton density[PD] and T2weighted) spin echo sequence (DE) (3mm axial slices;repetition time 3000 msec;echo times 36 and 162 msec; field of view 18cm; matrix 256x256, interleaved acquisition). The voxel (volume of pixel) dimensions for the fast gradient recalled acquisition were 0.7x0.7x1.5mm, and for the spin-echo acquisition they were 0.7x0.7x3 mm.

*Image Processing:*Postacquisition processing was carried out on a workstation (Sun Microsystems, Mountain View CA). A sequence of image processing algorithms was used to segment each of the MRI slices into separate tissue classes: cerebral cortical gray matter (GM), basal ganglia, myelinated white matter (MWM), unmyelinated white matter (UMWM) and cerebrospinal fluid (CSF)(5). These algorithms were designed to reduce imaging system noise, identify a linear transformation to align the DE spin-echo images with the fast-gradient recalled images to form a three-channel data set and resample the DE spin-echo images according to this transform. Tissue types were then classified on the basis of MR intensity in the three channels. A final summing of voxels for each tissue class was performed to compute absolute volumes. Relative volumes of the different tissues are reported as percentage of total intracranial volume. Comparison of relative volumes in the two groups was made using two-tailed *t*test.

Results

Quantitative assessment of neurostructural abnormalities in infants born with IUGR due to placental insufficiency revealed a significant reduction in cerebral cortical volume (see Tables). This reduction persisted after correction for size of intracranial volume (see Table). The subcortical gray matter structure of basal ganglia showed no significant volume difference nor did the degree of myelination vary between the two groups.

Discussion

These preliminary results indicate that placental insufficiency resulting in fetal IUGR has longterm consequences on cerebral cortical brain development. This disturbance might explain the high rate of cognitive dysfunction in this subpopulation of preterm infants.

References

1. Kok J, den Ouden A, Verloove-Vanhorick S, Brand R. Outcome of very preterm small for gestational age infants: the first nine years of life. Br J Obstet Gynaecol 1998; 105:162-168.

2. Alkalay A, Graham J, Pomerance J. Evaluation of neonates born with intrauterine growth retardation: review and practice guidlines. J Perinatol 1998; 18:142-151.

3. DeGruaw T, Myers R, Scott W. Fetal growth retardation in rats from different levels of hypoxia. Biol Neonate 1984; 46:10-13.

4. Cragg B. The development of cortical synapses during starvation in the rat. Brain 1972; 95:143-150

5. Huppi PS, Warfield S, Kikinis R, Barnes P, Zientara GP, JoleszFA, Tsuji MK, Volpe JJ. 3D-Visualization and Quantitation of the Developing Human Brain in Vivo. Annals of Neurology 1998; 43(2), 224-235.

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Brain Tissue Volumes

Brain Region		Normals	IUGR	p-value
Cortical GM	cc	216.7±24.1	132.5±19.7	<0.001
	%	43.9±1.78	33.47±5.3	<0.01
Basal Ganglia	cc	19.8±5.8	16.0±5.10	0.34
	%	4.1±1.5	4.0±1.1	0.71
MWM	cc	17.3±7.4	12.8±5.4	0.34
	%	3.4±1.1	3.2±1.1	0.76
UMWM	cc	198.9±49.6	191.5±39.8	0.81
	%	39.7±4.6	48.0±7.3	0.07
CSF	cc	42.6±19.8	44.7±4.8	0.84
	%	8.8±4.5	11.3±1.5	0.31
Total Intracranial Vol	cc	495.4±73.2	397.6±47.7	0.05