A 3D Volumetric study: Development of the hippocampus in Newborns with Intrauterine Growth Restriction

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Introduction:

The development of the hippocampus is vulnerable to a number of insults including hypoxia, undernutrition, stress and corticosteroids. Prematurity in itself has been shown to affect hippocampal growth in two different studies[1 2]. Hippocampal volume has been thoroughly investigated in adults with assessment of volume mostly by manual segmentation on MRI coronal images. There are no studies to this date on hippocampal volume in newborns.

Intrauterine growth restriction (IUGR) secondary to placental insufficiency remains an important cause of morbidity and long-term neurodevelopmental disability including memory impairment in children. It is a stressful situation for the fetus to grow in an environment chronically deprived from sufficient oxygen and nutrients. Dietary protein restriction further attenuates the expression 11 beta-hydroxysteroid-dehydrogenase type 2[3] in the placenta, which leads to increased fetal exposure to active glucocorticoids. We therefore hypothesized that intrauterine growth restriction with potential increase in exposure to glucocorticoids might affect the development of the hippocampus. Using 3-D volumetric MRI techniques, we studied the impact of IUGR on brain growth and in particular the hippocampal development in premature newborns with IUGR.

Methods:

Subjects. 11 preterm infants born with documented placental insufficiency (n=11, GA 32.3 wks ± 2.4, BW <10%tile 1170g ± 270) were compared with 11 preterm infants matched for gestational age at birth and with a normal growth (n=11, GA 32.1 ± 2.3wks, BW 1790 ± 390g, $p<0.001$).

MRI acquisition and processing. 3D volumetric MRI was performed at 40 weeks of gestation without sedation (IUGR: 40.4 ± 0.8 wks, Controls 40.4 ± 1.2wks, *ns*) using a 1.5T Marconi/Philips MR system. For the acquisition of the primary MR data, two different imaging modes were applied, a 3D-fast gradient echo sequence: coronal slices 1.5mm (TR=15 ms, TE=4.4 ms, Flip angle 25, FOV 18 cm), a Double-Echo (T2-and proton-density) fast spin-echo sequence: coronal slices 1.5 mm (TR=3500 ms, TE=30/150 ms, interleaved, no gap acquisition, FOV 18 cm). Post-acquisition image processing included linear registration of T2 coronal images on T1 coronal images. The determination of brain tissue volumes were then assessed using knn-algorithm on multiple channels (T2, T1, PD) including an anatomical template. A specially developed 3D rendering software, 3D Slicer (www.slicer.org), was used to visualize T2-weighted images in coronal, sagittal and axial plane, in order to manually segment the hippocampus. The tracing guidelines used in this study were published elsewhere[4-6]. We started manual segmentation on coronal slices. The boundaries of the head and tail of the hippocampus were outlined on the sagittal plane. Once the segmentation was achieved a 3D reconstruction was performed in order to check the quality of the segmentation (Figure 1). Hippocampal as well as intracranial volume was determined by summation of voxels. Intra-observer variability calculated on three hippocampal volumes segmented twice was 3.6%.

Statistics. A Wilcoxon matched pairs signed ranks test was used to compare the IUGR preterm group with the preterm group born appropriate for gestational age.

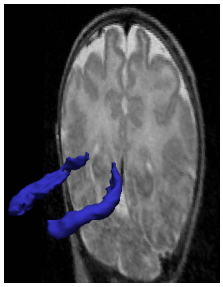

Figure 1

Results:

The overall hippocampal volume was found to be significantly smaller in the IUGR group (Table 1). Left and right hippocampal volumes analysed separately were also smaller in the IUGR group (Table 1). There was an overall right-greater-than-left asymmetry of the hippocampal volume (right hippocampus divided by left hippocampal volume: Median 109 % (Min 96% Max 124%) p = 0.008).

Discussion:

Experimental studies on IUGR have been shown to cause significant changes in brain structures affecting particulary hippocampal volume[7]. The alteration of the hippocampus in IUGR preterm children may be secondary to two potential mechanisms, chronic hypoxia as well as an increase in exposure to corticosteroids[8 9]. Different mechanisms by which glucocorticoids damage the hippocampus have been studied[10]. One of those is thought to be the activation of the glucocorticoid receptor (expressed in the dentate gyrus), leading to the expression of a pro-apoptotic protein bax [11].

	IUGR Mean volume (SD) (cc)	Control Mean volume (SD) (cc)	IUGR divided by its paired Control Median (Min - Max)
Total hippocampal volume	2.02 (0.22)	2.18 (0.16)	93% (82%-99%) **
Left hippocampal volume	0.96 (0.12)	1.05 (0.1)	92% (74% -103%)**
Right hippocampal volume	1.06 (0.12)	1.13 (0.07)	95 % (82% -104%)*

Table 1 Hippocampal volumes at 40 weeks. The Wilcoxon signed ranks test was used for group comparisons. * $p<0.05$; ** $p<0.01$

Conclusions

The overall volume of the hippocampus was found to be in the range of normative data established in children in the first year of life. An overall right-greater-than-left hippocampal volume asymmetry was found. Hippocampal volume was found to be significantly reduced in IUGR preterm infants compared to normal preterm infants at term. This volume reduction might be associated with learning and memory difficulties frequently observed in IUGR preterm infants.

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