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Cerebral volume at term age: Comparison between preterm and term-born infants using cranial ultrasound

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ABSTRACT

Background and aims: Very preterm infants are at particular risk of neurodevelopmental impairments. This risk can be anticipated when major lesions are seen on cerebral ultrasound (cUS). However, most preterm infants do not have such lesions yet many have a relatively poor outcome. Our study aims were to describe a tri-dimensional cUS model for measuring cranial and brain volume and to determine the range of brain volumes found in preterm infants without major cUS lesions at term equivalent age (TEA) compared to term-born control infants. We also aimed to evaluate whether gestational age (GA) at birth or being small for gestational age (SGA) influenced estimated brain size.

Methods: We scanned a cohort of very preterm infants at TEA and term-born controls. Infants with major cerebral lesions were excluded. Measurements of intracranial diameters (bi-parietal, longitudinal, cranial height), brain structures, ventricles and extracerebral space (ECS) were made. A mathematical model was built to estimate from the cUS measurements the axial area and volumes of the cranium and brain. Appropriate statistical methods were used for comparisons; a p-value under 0.05 was considered significant. SGA infants from both groups were analysed separately.

Results: We assessed 128 infants (72 preterms and 56 controls). The preterms' head was longer (11.5 vs. 10.5 cm, $p < 0.001$), narrower (7.8 vs. 8.4 cm, $p < 0.001$) and taller (8.9 vs. 8.6 cm, $p < 0.01$) than the controls'. Estimated intracranial volume was not statistically different between the groups (411 vs. 399 cm^3, NS), but preterms had larger estimated ECS volume (70 vs. 22 cm^3, $p < 0.001$), lateral ventricular coronal areas (33 vs. 12 mm^2, $p < 0.001$) and thalamo-occipital distances (20 vs. 16 mm, $p < 0.001$), but smaller estimated cerebral volume (340 vs. 377 cm^3, $p < 0.001$). Smaller brain volumes were associated with being of lower gestational age and birth weight and being small-for-gestational age.

Conclusions: We have developed a model using cranial ultrasound for measuring cranial and brain volumes. Using this model our data suggest that even in the absence of major cerebral lesions, the average extrauterine cerebral growth of very preterm infants is compromised. Our model can help in identifying those preterm infants with smaller brains. Later follow-up data will determine the neurodevelopmental outcome of these preterm infants in relation to their estimated brain volumes.

1. Introduction

Preterm infants are at significant risk of developmental disability. This risk increases with decreasing gestational age (GA) at birth [1]. Focal cerebral lesions identified on cranial ultrasound (cUS) are helpful in predicting types and severity of adverse outcomes, particularly motor deficits [2–4]. However, most preterm infants born at the present time do not have identifiable focal lesions on cUS [5] yet many have a relatively poor global outcome [6–8]. Determining which of these infants is at most risk of such neurodevelopmental disability remains a challenge for neonatologists.

Studying brain growth and development in preterm infants without focal brain lesions has been actively researched in recent years, almost exclusively using different magnetic resonance imaging (MRI) techniques, notably not only by defining smaller volumes of different cerebral structures at term equivalent age (TEA), but also by the use of advanced MRI techniques [9–14] that allow identification of poor cortical development [9], quantification of deep gray matter [12] and white matter maturation issues [14]. However, most of the above studies have been used to show group differences rather than giving information applicable to the individual infant. Also MRI is not widely available for

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clinical purposes in lower risk preterm infants, since it involves high costs, needs sedation in most cases, interpretation of more subtle findings is difficult and the relationship of such findings to outcome is not so well defined [10].

Some preterm infants without major central nervous system (CNS) lesions have smaller brains at TEA than term controls, even in the absence of overt brain injury [8,15,16]. It has been postulated that such infants may be at increased risk of neurodevelopmental disability [16–18]. Smaller brain volumes at TEA may not be a direct consequence of prematurity itself, but related to postnatal complications, e.g. prolonged oxygen requirement [19], high *Clinical Risk Index for Babies* (CRIB) score, high C reactive protein and time to achieve full enteral feeds [20].

A qualitative cUS approach detecting poorer brain growth at TEA has been related to poorer outcomes [18], but to the best of our knowledge quantitative approaches using cUS have not been used to address this issue.

We aim to (1) develop a model for estimating cranial and brain volumes using measurements made from cranial ultrasound imaging, (2) assess the reliability of our measurements and (3) determine whether using this model would allow us to find expected differences in brain volumes between preterm infants at TEA and newborn full-term control infants and between appropriate and small-for-gestational age infants at TEA.

2. Methods

We assessed prospectively during a 28 month period (May 2008–August 2010): (1) a consecutive cohort of preterm infants born at <32 weeks GA and scanned using cUS at TEA; and (2) a group of term-born control infants scanned during the first postnatal week.

The study was performed at the Hospital de Santa Maria in Lisbon, a tertiary Neonatal Intensive Care Unit (NICU) and main referral centre for south Portugal. Written informed parental consent was obtained for each case and control infant; the study was approved by the Medical Ethics Committee of the Hospital de Santa Maria.

Preterm infants with neurological problems or scan abnormality except isolated germinal layer haemorrhage or transient periventricular flares (known to be transient as infants were scanned regularly from birth until TEA) were excluded from the study. No infant had hydrocephalus or marked ventriculomegaly. Small-for-gestational age (SGA) infants (birth weight <10th centile on the updated Babson and Benda's charts [21]) were analysed separately.

The term control infants were well newborns; some had jaundice, were being given antibiotics for suspected but unproven sepsis or had mild and transient respiratory distress. Median Apgar scores were 9 at 1 min and 10 at 5 min. None had abnormality detected on the cUS done for the purposes of this study and none had neurological problems. They were born during the study period and remained in the hospital for at least 72 h.

All cUS images were acquired by one author (AG) using a Siemens Acuson Sequoia® scanner (10v4 transducer set to 8.5 MHz) as part of the NICU's standard scanning protocol. The images were transferred to a workstation and the measurements of bi-parietal diameter, longitudinal intracranial diameter, cranial height, brain structures, ventricles and extracerebral space (ECS) were made using ImageArena® 2.9 software according to previously described measurements when available [22–28] (Fig. 1, Table 1). Control term-born infants were not scanned within the first 72 h after birth to allow time to minimize head moulding effects on the measurements.

A mathematical model was built to estimate, from the cUS measurements, the axial area and volumes of the cranium and brain; this model (Fig. 2) is based on five assumptions:

(1) The 3 cranial radii considered for the model (Fig. 2) were half of the intracranial bi-parietal diameter (R1 = BPD / 2), the intracranial antero-posterior or occipito-frontal diameter (R2 = APD / 2) and the intracranial cranial height (R3 = CH / 2). Bone was not included in these measurements;
(2) The axial plane of the cranium at the level of the maximal occipital-frontal circumference (OFC) was considered an ellipse for area estimation (area = $\pi * R1 * R2$);
(3) The cranium was considered as an ellipsoid for volume estimation (volume = $4/3 * \pi * R1 * R2 * R3$);
(4) The depth of the ECS, measured bilaterally from the edge of the sagittal sinus to the surface of the cortex in a coronal plane at the level of the foramen of Monro [27,28] would give a mean estimate of the whole ECS. This site was chosen on the assumption that at this point the width of the ECS is intermediate between the more anterior anterior and posterior widths, and representative of the whole ECS;
(5) The 3 estimated radii of the brain (RR1, RR2, and RR3) would be obtained by subtracting the ECS from the 3 cranial radii (R1, R2, and R3) (Fig. 2).

Statistical comparison for numerical variables was performed using independent samples *t*-test or the Mann–Whitney test as appropriate after assessing normality of each group and each variable using the Shapiro–Wilk test. The potential effect of numerical co-variates was assessed using ANCOVA analysis after testing for necessary assumptions: normality (Shapiro–Wilk test) and homogeneity of regression (slope). Multiple group comparisons were performed using analysis of variance (ANOVA) with Hochberg post-hoc analysis after verifying homogeneity of variances using the Levene test. Correlations were calculated using the Pearson correlation for normal variables and the Spearman correlation for variables that do not follow a normal distribution. Categorical variables were compared using the chi-square test. Differences were considered significant when the p-value was <0.05. SPSS 19® statistical software was used for all the statistical analyses.

The intra- and inter-observer reliability of the linear cUS measurements was tested using intraclass correlation coefficient (ICC) with the strength of agreement scale described by Brennan [29]. Accuracy was considered good for an ICC of between 0.61 and 0.80 and very good for an ICC above 0.80.

3. Results

We assessed 128 infants, 72 preterms at TEA and 56 term infants during their first postnatal week (Table 2). The preterm infants were of significantly lower birth weight, were more often born by caesarean section, had lower Apgar scores and higher CRIB scores than the control group. No infant in the control group was invasively ventilated or had culture-proven sepsis. In contrast 44% of the preterm infants were invasively ventilated, and 28% of them had at least one episode of culture-proven sepsis. No significant differences between the groups were found for gender or being SGA at birth.

All preterm infants were scanned between 36 and 44 weeks PMA. There was a small non-significant difference of 3.4 days in PMA at scan between the preterm and term control infants (Table 2).

Although the preterm infants weighed less and were shorter than the control infants at scan date, their mean OFC was larger (Table 2). The characteristic shape of the preterm infants' head at TEA could be demonstrated numerically (Table 3), as their heads were significantly longer (11.5 vs. 10.5 cm, $p < 0.001$), narrower (7.7 vs. 8.4 cm, $p < 0.001$) and taller (8.9 vs. 8.6 cm, $p < 0.01$) than in the term controls. By applying a two-dimensional elliptical model to the linear measurements of cranial length and width, we found that despite the larger OFC in the preterm group, the cranial area in the plane of the maximum occipito-frontal diameter was not significantly different from the term born controls (69.3 vs. 69.5 cm^2, NS) (Table 4).

Most CSF spaces were larger in the preterm infants at TEA than in the term infants (Table 3), most notably the ECS and the lateral