Recovery of Head Circumference Z-Score in Healthy Very Preterm Infants at Term-Equivalent Age Does Not Reflect Adequate Brain Growth

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Abstract

Introduction: Head circumference is widely used as a marker of brain growth in very preterm infants. We aimed to evaluate the progression of head circumference, extra-cerebral space, and estimated brain volume of very preterm infants between birth and term equivalent age compared to term-born controls.

Methods: We assessed prospectively a cohort of infants born at ≤ 32 weeks gestation and term control newborns. Infants with cerebral abnormalities were excluded. Head circumference was measured at birth and at term equivalent age in preterm infants and at birth in term infants. Extra-cerebral space and estimated brain volume were estimated by a previously described ultrasonography model applied on cranial ultrasounds performed during the first days of life (preterms and controls) and at term equivalent age (preterms). *Z*-scores for head circumference were determined using Fenton growth charts and *z*-scores for extra-cerebral space and the estimated brain volume was defined in controls.

Results: We assessed 105 infants (49 preterms and 56 controls). Head circumference *z*-scores increased significantly between birth and term equivalent age and were identical to controls at term equivalent age. Extra-cerebral space *z*-scores increased significantly between birth and term equivalent age and were higher at the term equivalent age in preterm infants compared to controls. Estimated brain volume *z*-scores in preterm infants decreased significantly between birth and term equivalent age.

Discussion: Normal head circumference *z*-score of healthy preterm infants at a term equivalent age does not reflect a brain sparing effect, as it is mainly due to an increase in extra-cerebral fluid rather than brain volume. Caution is advised when using head circumference as a marker of adequate brain growth in very preterm infants, particularly when discussing outcomes with parents.

Keywords: Brain/growth & development; Cranial ultrasound; Cephalometry; Child Development; Head/growth & development; Infant, Extremely Premature/growth & development

Introduction

Preterm infants are known to be at significant risk of poor neurodevelopmental outcomes[1] and this risk is well established in those with major central nervous system lesions.[1-4] However, even preterm infants without major neonatal morbidities have been shown to carry an increased risk of cognitive and motor difficulties.[5] However, there is still a lack of a sensitive screening tool to determine which of these infants are most at risk and will require closer surveillance.

It has been shown that even in the absence of major cerebral lesions, the average extra-uterine cerebral growth of very preterm infants is compromised.[6-11] Many factors have been implicated, including nutritional deficits, environmental factors, postnatal decrease in circulating insulin-like growth factor-I, and patent *ductus arteriosus*.[7,12-14]

Low cerebral volumes at term age, as has been shown with magnetic resonance imaging (MRI) based studies, are linked to poorer developmental outcomes and neuropsychiatric disorders,[5,15,16] and have become a promising prognostic marker.

Head circumference measurement is a non-invasive, easy, and widely used method that is thought to correlate well to brain volume. Studies have shown that there is a strong correlation between microcephaly and low brain volumes in very preterm infants at term equivalent age,[6,17] which is associated with poorer cognitive and motor development at 2 years and an increased rate of cerebral palsy.[17]

Our group previously described a tri-dimensional model for estimating cranial and brain volume using cranial ultrasonography.[11]

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In this study, we aim to evaluate the progression of head circumference (HC), extra-cerebral space (ECS), and estimated brain volume (EBV) of very preterm infants from birth to term equivalent age (TEA) and compare them to the ones of term-born control infants.

Methods

We assessed prospectively, along a 28-month period, a consecutive cohort of preterm infants born at ≤ 32 weeks gestational age and a group of healthy term control newborns.

The study was performed in the neonatal intensive care unit (NICU) of a tertiary hospital. Written informed consent was obtained from the parents of the enrolled infants.

Preterm infants with neurological problems or scan abnormalities were excluded from the study, except for isolated germinal layer hemorrhage or transient periventricular flares (known to be transient, as infants were scanned regularly from birth until term equivalent age). No infant had hydrocephalus or significant ventriculomegaly.

Head circumference was measured both at birth and at term equivalent age in preterm infants, and at birth in term newborns.

Cranial ultrasonography was performed during the first days of life, in both preterm infants and controls, and at term equivalent age (between 36 and 44 weeks of postmenstrual age) in preterm infants.

Z-scores for head circumference were determined using Fenton 2013 growth charts, and *z*-scores for extra-cerebral space and estimated brain volume were defined in the controls.

Statistical analysis was conducted using SPSS 20.0®. Categorical variables were compared using the chi-square test. A comparison of numerical variables was performed using either the independent *t*-test or Mann-Whitney test, according to the normality of variables. The differences were considered significant when *p*-value was < 0.05.

Results

We assessed 105 infants, 49 preterm infants, and 56 controls. Preterm infants had a significant lower birth weight, were more often born by caesarian section and had lower Apgar scores. There were no significant differences between groups regarding gender or being small for gestational age. None of the infants in the term-born group were invasively ventilated or had culture proven-sepsis, while preterm infants had a 49% rate of invasive ventilation use and 31% had at least one episode of culture-proven sepsis (Table 1).

Head circumference

In preterm infants, head circumference *z*-scores increased significantly between birth and term equivalent age. At term equivalent age, no significant differences were found relative to term controls (Table 2, Fig. 1).

Volume estimates

Extra-cerebral space and estimated brain volume were estimated from cranial ultrasonography images using a previously described tri-dimensional model.[11] Extra-cerebral space *z*-scores of preterm infants increased significantly between birth and term equivalent age and were significantly higher at term equivalent age than in controls (Table 2, Fig. 2). In contrast, estimated brain volume *z*-scores decreased significantly from birth to term equivalent age and were significantly lower at term equivalent age than in controls (Table 2, Fig. 3).

Table 1. Comparison of the perinatal characteristics between preterm and term infants

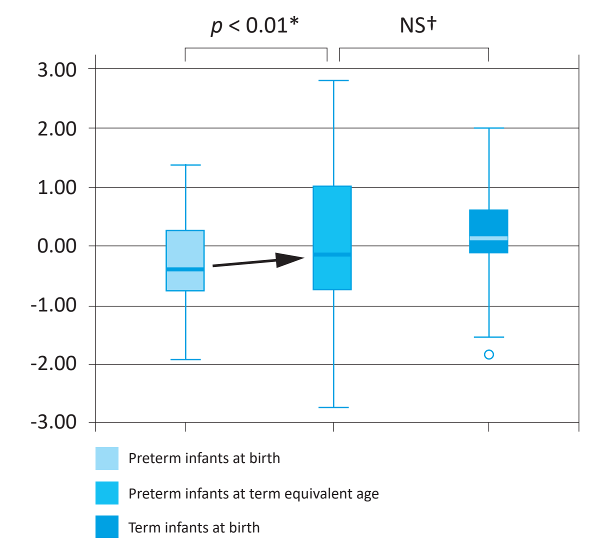
	Preterm	Term	*p*
n	49	56	
Birth weight (grams)*	1066 (510-1505)	3191 (2385-4445)	< 0.001
Gestational age (weeks)†	28.6 (24-32)	39.2 (37-42)	< 0.001
Small for gestational age‡	14%	13%	NS
Male gender‡	57%	61%	NS
Caesarian section	71%	53%	< 0.005
Apgar score at 1 minute§	8 (1-10)	9 (3-10)	< 0.001
Apgar score at 5 minutes§	10 (6-10)	10 (8-10)	< 0.005
Invasive ventilation‡	49%	0%	< 0.001
Sepsis (culture-proven)‡	31%	0%	< 0.001

NS – nonsignificant.
* Presented as mean (range), statistical analysis using the Mann-Whitney test.
† Presented as mean (range), statistical analysis using the independent samples *t* test.
‡ Presented as percentage, statistical analysis using Pearson's chi-square test.
§ Presented as median (range), statistical analysis using the Mann-Whitney test.

Table 2. Comparison of the measurements of preterm (at birth and term equivalent age) and term infants

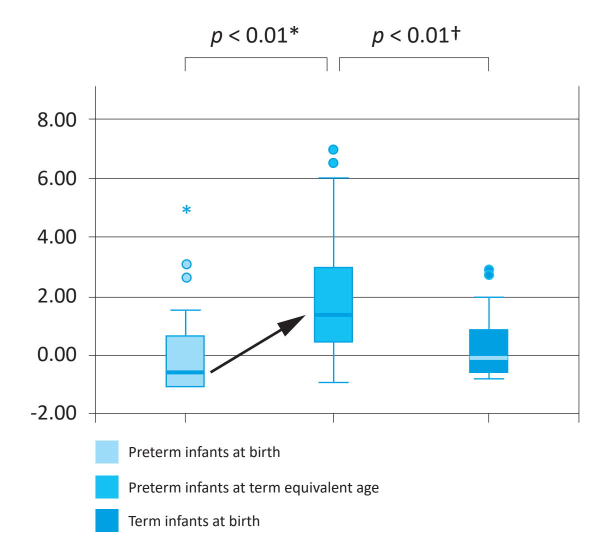
	Preterm at birth	Preterm at TEA	*p*	Term	*p*
n	49	49		56	
Age at scan (days)	4 (0-9)	81 (55-117)	< 0.001*	5 (2-9)	< 0.001†
HC *z*-score	-0.31 (-1.96-1.49)	0.17 (-2.72-2.82)	0.002‡	0.27 (-1.86-1.93)	NS§
ECS *z*-score	0.00 (-0.6-4.3)	1.84 (-1.00-6.70)	< 0.001*	0.00 (-1.00-2.90)	< 0.001†
EBV *z*-score	-0.04 (-1.80-1.87)	-0.99 (-3.09-1.58)	< 0.001‡	0.00 (-2.06-2.22)	< 0.001§

EBV - estimated brain volume; ECS - extra-cerebral space; HC - head circumference; NS - nonsignificant; TEA - term equivalent age.
* Presented as mean (range), statistical analysis using the Mann-Whitney test.
† Presented as mean (range), statistical analysis using the independent samples *t* test.
‡ Presented as percentage, statistical analysis using Pearson's chi-square test.
§ Presented as median (range), statistical analysis using the Mann-Whitney test.



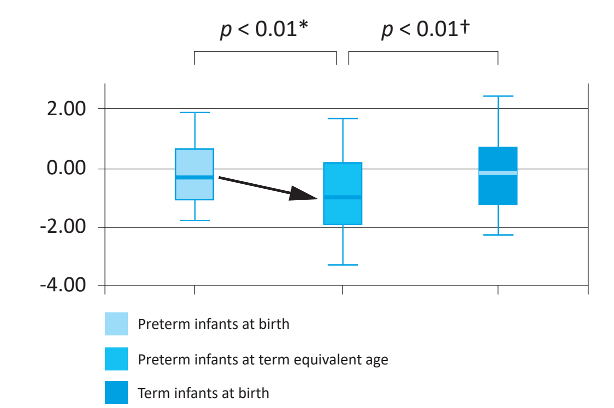
* Pearson's chi-square test.
† Mann-Whitney test.
Significance level $p < 0.05$.

Figure 1. Boxplot of *z*-scores for head circumference in preterm infants at birth and term equivalent age, and term newborns at birth.



* Pearson's chi-square test.
† independent samples *t* test.
Significance level $p < 0.05$.

Figure 2. Boxplot of *z*-scores for extra-cerebral space in preterm infants at birth and term equivalent age, and term newborns at birth.



* Pearson's chi-square test.
† Mann-Whitney test.
Significance level $p < 0.05$.

Figure 3. Boxplot of *z*-scores for estimated brain volume in preterm infants at birth and term equivalent age, and term newborns at birth.

Discussion

Our study shows that cerebral volumes measured by cranial ultrasonography in very preterm infants at term equivalent age are lower than the ones of term-born controls. This finding has been previously reported in MRI-based studies,[5,11,15,18] some of which show that brain volume alterations in lower gestational age infants at term equivalent age differ in magnitude across different brain regions.[19-21] However, due to improvements in neonatal care, there is an increasing number of very preterm infants who reach term equivalent age without major central nervous system lesions visible on cranial ultrasonography, and most centers do not routinely perform brain MRI under such circumstances (due to high costs, low availability, sedation-associated risks, and absence of unequivocal value for prognosis). Nevertheless, this approach is questioned by some experts in this field, who recommend the proper documentation of their brain status by MRI prior to discharge from the neonatal intensive care unit.[22]
Low head circumference is known to correlate well to low brain volume at term equivalent age.[6,17] However, our results show that a normal head circumference

at term equivalent age does not preclude low brain volume, since very preterm infants, despite having comparable head circumference *z*-scores, had significantly lower estimated brain volumes than term-born controls. This finding suggests that the recovery of head circumference *z*-scores in healthy very preterm infants at term equivalent age does not reflect a brain sparing effect as it is mainly due to an increase in extra-cerebral fluid rather than an increase in brain volume. Direct measurement of brain volume, using an imaging study, could increase sensitivity in determining neurodevelopmental prognosis.

Cranial ultrasonography is an inexpensive, non-invasive, accessible, and routinely performed exam at term equivalent age that has shown promising results in quantifying brain volume at term equivalent age using the tri-dimensional model applied to this study.[11]

Long-term follow-up studies are required to establish the correlation between measurements of cerebral volume by this method and neurodevelopmental outcome. If such correlation is verified, the cerebral volume measurement by cranial ultrasonography at term equivalent age could become a useful and widely available tool to further increase sensitivity in determining neurodevelopmental prognosis at an early age.

In summary, we found similar head circumferences but significantly lower cerebral volumes in preterm infants at term equivalent age compared to term-newborns, revealing the need to take caution when using head circumference as a marker of adequate brain growth, particularly when discussing outcomes with parents. This leads us to hypothesize that the direct measurement of cerebral volume may be a better marker for neurodevelopmental outcome and that cranial ultrasonography, as an easy, non-invasive, accurate technique, may be the most practical imaging method to assess it.

WHAT THIS STUDY ADDS

- Normal head circumference at term-equivalent age does not preclude inadequate brain growth.
- Very preterm babies at term-equivalent age have similar head circumference *z*-scores but lower brain volumes than term-born controls.
- Recovery of head circumference *z*-scores in healthy preterm infants at term-equivalent age occurs mainly due to an increase in extra-cerebral fluid rather than an increase in brain volume.
- Caution should be taken when using normal head circumference as a marker of adequate brain growth in preterm infants.
- Brain volume estimation by cranial ultrasound could become a useful and accessible tool for the assessment of neurological prognosis.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Provenance and peer review

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Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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A Recuperação do Z-Score do Perímetro Cefálico em Recém-Nascidos Grandes Pré-Termos Saudáveis na Idade Equivalente a Termo Não Reflete Adequadamente o Crescimento Cerebral

Resumo:
Introdução: O perímetro cefálico (PC) é usado frequentemente como marcador do crescimento cerebral em grandes prematuros (PT). O objetivo deste trabalho foi avaliar a progressão do PC, espaço extra-cerebral (EEC) e volume cerebral estimado (VCE) de grandes PT entre o nascimento e a idade equivalente ao termo (IET) e compará-los na IET com os de recém-nascidos (RN) de termo saudáveis.
Métodos: Foi avaliada prospectivamente uma coorte de RN com idade gestacional ≤32 semanas e um grupo controlo de RN de termo. Foram excluídos RN com lesões cerebrais significativas. No grupo de grandes PT, o PC foi medido ao nascer e na IET, e no grupo controlo foi medido ao nascer. O EEC e VCE foram estimados por um modelo ecográfico previamente descrito (Graça AM, Early Hum Dev 2013) aplicado em ecografias cerebrais transfontanelares realizadas nos primeiros dias de vida (PT e controlos) e na IET (PT). Os Z-scores para o PC foram determinados através das curvas de crescimento de Fenton 2013 e os Z-scores do EEC e VCE foram determinados através dos controlos.
Resultados: Foram avaliados 105 RN (49 PT e 56 controlos). Nos PT, o Z-score do PC aumentou significativamente entre o nascimento e a IET e, na IET, foi idêntico ao de RN de termo. O Z-score do EEC aumentou significativamente entre o nascimento e a IET e foi superior na IET em comparação com RN de termo. O Z-score do VCE em PT diminuiu significativamente entre o nascimento e a IET.
Conclusão: Um Z-score do PC normal em PT saudáveis na IET não reflete necessariamente um crescimento cerebral adequado, uma vez que este parâmetro aumenta sobretudo à custa do líquido extra-cerebral, e não do volume cerebral. O PC deve ser usado com cautela enquanto marcador de crescimento cerebral adequado em grandes PT, particularmente na discussão do prognóstico com os pais.

Palavras-Chave: Cabeça/crescimento & desenvolvimento; Cefalometria; Cérebro/crescimento & desenvolvimento; Desenvolvimento Infantil; Ecografia cerebral transfontanelar; Lactente Extremamente Prematuro/crescimento & desenvolvimento