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Growth in very preterm children: Head growth after discharge is the best independent predictor for cognitive outcome

Karen Lidzba, PhD [a,*], Susanne Rodemann, M.D. [a], Rangmar Goelz, M.D. [b], Ingeborg Krägeloh-Mann, M.D., PhD [a], Andrea Bevot, M.D. [a]

[a] University Children's Hospital Tübingen, Department of Pediatric Neurology and Developmental Medicine, Hoppe-Seyler-Str. 1, 72076 Tübingen, Germany
[b] University Children's Hospital Tübingen, Department of Neonatology, Calwerstr. 7, 72076 Tübingen, Germany

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ABSTRACT

Background: The contribution of growth parameters to the cognitive outcome of very low birth weight (VLBW)/very preterm (VP) infants is difficult to disentangle from other preterm-birth related factors.
Aims: We hypothesized that long-term cognitive and motor outcome of VLBW/VP infants is most strongly associated with growth in head circumference after hospital discharge.
Study design: Single-centre prospective longitudinal study: anthropometric measures at different time points (birth, discharge, school-age).
Subjects: 136 VLBW/VP infants (<32 weeks gestation/birth weight < 1.500 g).
Outcome measures: Cognitive and motor function (Kaufman Assessment Battery for Children; Movement Assessment Battery for Children) at school-age (6.7–10.0 years, mean = 8.2).
Results: In hierarchical multiple regression analyses, growth from birth to discharge significantly predicted cognitive outcome (weight: $R^2_{change} = 0.063$, $p = 0.014$; length: $R^2_{change} = 0.078$, $p = 0.007$; HC: $R^2_{change} = 0.050$, $p = 0.030$), as well as weight gain ($R^2_{change} = 0.096$, $p = 0.001$) and head growth ($R^2_{change} = 0.134$, $p < 0.001$) from discharge to school-age. While most growth parameters, especially those from birth to discharge, were significantly influenced by prenatal growth and immaturity related morbidity ($R^2 = 0.151$ to 0.605, all $p \leq 0.001$), head growth after discharge was not ($R^2 = 0.029$, $p = 0.461$).
Conclusions: Amongst all anthropometric measures, head growth between discharge and school-age is the best independent predictor for cognitive outcome in VLBW/VP infants. Determinants of head growth after discharge need further studies to identify targets for intervention.

1. Introduction

1.1. Growth in preterm infants

Very or extremely low birth weight preterm infants (VLBW; ELBW) are at risk for impaired physical growth: Up to 40% are born small for gestational age (SGA) when compared to foetuses in utero [1], indicating sub-optimal nutritional supply already prenatally. They continue to be at risk for impaired growth during hospitalization [2], childhood [3], and adolescence [4]. Preterm infants born SGA demonstrated delayed cognitive development into the preschool [5,6] and early school years [7], especially if SGA birth was followed by postnatal failure to thrive [8]. Across the group of preterm infants, early postnatal growth (i.e., during hospitalization) has been associated with neurological and cognitive outcome in infancy and preschool-age [9–12].

1.2. Growth and cognitive development

Amongst the parameters of physical growth, i.e., weight, length, and head circumference (HC), HC seems to be the principal determinant of cognitive and, less consistently, motor development [13,14]. Catch-up growth during the first post-term months of life [15–17] and during childhood [18] was positively correlated with later cognitive development. Recent publications report that antenatal head growth in preterm-born infants was only little related to preschool cognitive performance, while a positive association has been shown for head growth between birth and two years [19], and between birth and five

Abbreviations: BPD, bronchopulmonary dysplasia; CP, cerebral palsy; ELBW, extremely low birth weight; HC, head circumference; ICH, intracranial haemorrhage; K-ABC, Kaufmann Assessment Battery for Children; M-ABC, Movement Assessment Battery for Children; MPC, Mental Processing Composite; SDS, standard deviation score; SGA, small for gestational age; TIS, total impairment score; VP, very preterm; VLBW, very low birth weight.

* Corresponding author.
E-mail addresses: karen.lidzba@med.uni-tuebingen.de (K. Lidzba), susanne.rodemann@freenet.de (S. Rodemann), rangmar.goelz@med.uni-tuebingen.de (R. Goelz), ingeborg.kraegeloh-mann@med.uni-tuebingen.de (I. Krägeloh-Mann), andrea.bevot@med.uni-tuebingen.de (A. Bevot).

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years of age [20]. This suggests that head growth beyond discharge from the neonatal unit may play a decisive role for cognitive development.

1.3. Factors influencing growth in preterm infants

The growth of preterm infants is influenced by a complex conglomerate of interrelated factors, mainly immaturity, morbidity, and nutrition [2,14,21,22]. Both immaturity and morbidity, however, are widely accepted to also determine the preterm infant's developmental outcome [23–25]. Impairment in postnatal growth and in cognitive development could, therefore, be the effect of the same causal variables, namely, immaturity at birth and/or neonatal morbidity. The preterm infant's nutrition has received much interest and the introduction of special preterm formulas has significantly improved preterm infants' early weight gain [22] and cognitive outcome [26]. Currently, there is an ongoing endeavour to further optimize preterm nutrition by setting standards for individualized nutritional care [27]. While there is evidence that increased nutrition during hospital stay may increase the likelihood of survival without neurodevelopmental impairment, the direct relationship between early nutrition and neurodevelopmental outcome remains elusive [28]. Disentangling the unique contribution of growth during different phases from the effects of immaturity and morbidity could help to better identify targets for nutritional intervention.

1.4. Study scope and hypotheses

The aim of our study was to investigate the relationship between growth and cognitive/motor development at early school-age. We postulated that (H1) growth, and more specifically, head growth after discharge has more influence on cognitive and motor development until early school-age than anthropometric measures at birth or growth during hospital stay. Beyond that, we hypothesized that (H2) growth during hospital stay is largely determined by anthropometric measures at birth, immaturity and morbidity.

2. Patients and methods

2.1. Patients

All 141 participants took part in a prospective follow-up study aiming to investigate the relationship between growth and cognitive and motor development in a cohort of very preterm (VP)/very low birth weight (VLBW) infants (<32 weeks gestation or <1.500 g) born between 07/01/1995 and 12/07/1997, treated in one neonatal intensive care unit of a tertiary centre (University Children's Hospital, Tübingen, Germany). At school-age follow-up, the children were between 6.7 and 10.0 years old (mean [SD] = 8.23 [0.74] years).

2.2. Anthropometry

Anthropometric data (body length, weight, and HC) were measured at birth, on the day of discharge and on the day of follow-up examination, using suitable equipment for infants or children [29]. The largest possible (fronto-occipital) circumference was measured with a flexible, but not extensible tape (measuring error 0.3–0.4 cm) [29,30]. The anthropometric measurements were expressed in standard deviation scores (SDS) = (subject parameter − reference mean) / (reference standard deviation). At birth and discharge, the references of Niklasson [31] were used, adapting the data to gestational age until 42 weeks. At school-age, the Swiss standard charts by Prader [32] were used as references, since they best reflect the regional population.

Catch-up growth from birth to discharge ($SDS_{D\text{-}B}$) was defined as difference between age-standardized measures at discharge (SDS_D) and age-standardized measures at birth (SDS_B). Catch-up growth from discharge to school-age ($SDS_{S\text{-}D}$) was defined as difference between standardized measures at school-age (SDS_S) and at discharge.

2.3. Neurological examination and assessment of neuromotor function

Neurological status at follow-up was classified as abnormal when cerebral palsy (CP; definition according to Surveillance of Cerebral Palsy in Europe [33]) was present. Children with CP were excluded. Neuromotor function was assessed with the Movement Assessment Battery for Children (M-ABC) [34]. This test comprises eight tasks measuring manual dexterity, ball skills, and balance. Raw scores range from zero to five, zero indicating no impairment. The sum of all scores constitutes the total impairment score (TIS).

2.4. Assessment of cognitive function

Cognitive function was assessed with the Kaufmann Assessment Battery for Children (K-ABC) [35]. This test battery assesses cognitive functioning in children aged 3 to 12 years. The Mental Processing Composite Score (MPC) is calculated from the simultaneous processing scale (visuo-spatial and logical abilities) and the sequential processing scale (measuring auditory and visual short term memory and attention).

2.5. Socio-economic status and parental education

Maternal education is considered the strongest socio-economic predictor for intelligence in children born preterm [36]. Thus, we extracted the data on maternal education from a standardized questionnaire on parental education and socio-economic status (Hoffmeyer-Zlotnik-Index [37]). Maternal education is expressed in an ordinal scale on education and professional qualification ranging from one (lowest) to eight (highest).

2.6. Statistical analysis

To test hypothesis H1, we conducted three sets of independent hierarchical multiple regression analyses for weight, length, and HC. To reduce collinearity within the model, the multiple confounding factors related to preterm birth (gestational age, bronchopulmonary dysplasia (BPD; yes/no), days of ventilation, postnatal corticosteroids (yes/no), intracranial haemorrhage (ICH; grade I–IV), sepsis (yes/no)) were first subjected to a principal axis factor analysis with varimax-rotation, resulting in one factor ("immaturity": gestational age, days of ventilation, corticosteroids, BPD). Standardized factor scores (large scores implicating high degree of immaturity) were calculated with the Anderson-Rubin-Method. Since neither ICH nor sepsis correlated with the other variables, they were retained as independent predictors. Analyses were conducted with K-ABC MPC or M-ABC TIS as dependent variables, and potential confounding factors (maternal education, "immaturity", ICH, sepsis), anthropometric data at birth (SDS_B), growth between birth and discharge ($SDS_{D\text{-}B}$), and growth between discharge and school-age (SDS_S) as predictors introduced in a hierarchical manner. To test hypothesis H2, we conducted independent simultaneous regression analyses with "immaturity", ICH, and sepsis as predictors, and growth data ($SDS_{D\text{-}B}$; $SDS_{S\text{-}D}$) as outcome.

2.7. Ethics

The internal review board of University Tübingen's Medical Faculty approved of the study. Informed consent was obtained from the parents, and children assented to the procedures performed at school-age.

3. Results

Table 1 lists the cohort's demographic, pregnancy-/birth-related and neonatal characteristics. In the neurological examination, 130 (92%) of the children were rated as normal, six as clumsy (4%), and five (4%) were excluded from further analyses due to CP.