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Original Research Article

Growth in Infancy Following Extremely Premature Birth: Associations with Later Neurodevelopmental and Health Outcomes

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Abstract

Objective: Premature birth causes the brain to be prematurely exposed to the extrauterine environment during a crucial time for neurodevelopment. As a result, preterm babies are more likely to experience negative behavioral outcomes in adulthood. The aim was to examine the relationship between postnatal growth and neurodevelopment in very low gestational age infants (ELGAN, 27 weeks' gestation) at the age of 1 years.

Method: Live ELGAN born in June 2021– July 2022, at Department of Paediatric, MGM Medical College and LSK Hospital, Kishanganj, were included in a retrospective population-based cohort study. 250 infants in all made it out of the hospital and were taken into account in the studies. For 150 newborns, FU1 was recorded.

Results: At 2FU, the average (±SD) psychomotor and mental development indices were 86.8 (±17.6) and 88.8 (±18.1), respectively. 23.1% of patients had moderate or severe neurodevelopmental impairment identified. Weight z-scores between birth and discharge and between birth and FU1 changed by 1.05 (±0.84) and 0.141 (±1.14), length z-scores changed by 1.35 (±1.33) and 0.41 (±1.32), head circumference z-scores changed by 0.60 (±1.03) and 0.75 (±1.31), and BMI z-scores changed by 0.21 (±3.35) and 0.005 (±1.44). No one of the four growth indicators was significantly correlated with any of the three neurodevelopmental outcome parameters, according to both unadjusted and adjusted analyses. This held true for both time periods.

Conclusion: Neither growth between birth and hospital discharge nor growth between birth and FU1 were significantly linked with neurodevelopment at the age of one year in the current population-based cohort of ELGAN.

Keywords: Neonatal Growth, Neurodevelopment, FU1.

Introduction

In the globe, 10% of babies are born prematurely (less than 37 weeks gestation) [1] and 0.5% are ELGANs (neonates born at <28 0/7 weeks of gestation) [2]. Over the past few decades, significant improvements in these patients' survival rates have resulted in lower mortality rates, but the risk of delayed cognitive and motor development is still very high [3]. In addition to affecting children from birth, impairment also has a significant detrimental effect on later-life mental health, academic success, and school performance [4].

Despite the fact that a number of risk factors have been identified, including short gestational age, brain lesions, bronchopulmonary dysplasia, and confirmed sepsis [8], studies on the relationship between postnatal growth and neurodevelopment have produced conflicting results [5]. From early childhood through adulthood, malnutrition is linked to impaired neurodevelopment [Figure 1; 7] and decreased head growth is linked to impaired neurodevelopment [6].

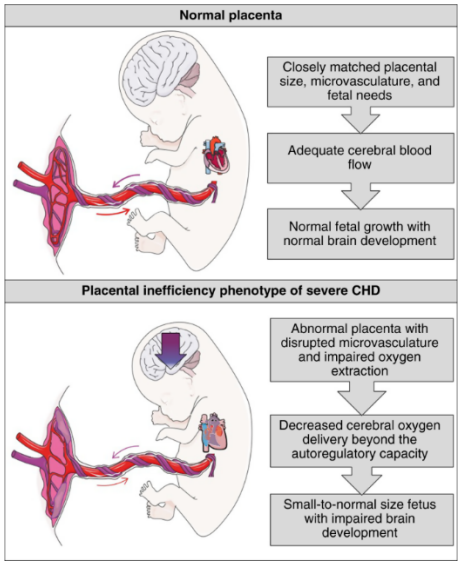

Figure 1: association between increased head growth and impaired neurodevelopment

Nonetheless, there is still disagreement regarding how postnatal growth affects neurodevelopment. While increasing caloric intake seems to promote growth, it may also have long-term negative health effects, such as an increased risk of developing metabolic syndrome as adults, as well as increased body fat without improving lean body mass [8].

In order to determine if somatic growth during NICU stays and during the first year of life is connected with neurodevelopmental outcomes at the age of one year, a retrospective, population-based analysis of a sizable cohort of ELGAN was done.

Methods

Study Design: This study is a retrospective population-based cohort that includes live births that occurred in the Department of Paediatric, MGM Medical College and LSK Hospital, Kishanganj between June 2021 and July 2022.

Methodology: The SNN prospectively gathers follow-up information on perinatal, neonatal, and neurodevelopmental outcomes for live births with a gestational age between 21 and 31 weeks or a birth weight of 1500 g.

It has been suggested that preterm infants born at 31 weeks of gestation should have a

neurodevelopmental follow-up at a corrected age of 19 to 25 months (1-year follow-up, FU1). The anthropometric measurements—weight, length, head circumference, and body mass index—were taken at birth, when the baby was sent home (rather being transferred between hospitals), and at FU1. Neonatal and FU1 measurements were recorded as z-scores and absolute values. Further demographic, perinatal, and neonatal baseline factors have been defined, including gestational age and significant newborn morbidities indicated in the results section and the supplemental material. Significant brain lesions were classified as either cystic PVL or IVH grades III or IV.

Exclusion criteria: infants with major congenital anomalies (genetic anomaly or syndrome, malformation of a major organ system, or other congenital conditions that could affect life expectancy or neurodevelopment), infants receiving palliative care or primary non-intervention at birth, and infants who passed away before being released from the hospital.

Statistical analysis*:* Main and secondary analyses evaluated the relationship between development at FU1 and growth from birth to FU1 (delta2) and from birth to hospital discharge (delta1), respectively. Post hoc calculations were made to determine the relationship between the absolute anthropometric measurements at birth, hospital discharge, and FU1.

Eight growth variables were created by taking into account four (continuous) growth factors during the two period's delta1 and delta2. These factors were body weight, length, head circumference, and BMI.

We examined two additional outcomes from BSID-II (the mental and psychomotor development index, MDI, and PDI), as well as one binary outcome (NDI). There were 24 analysed associations as a result. While all infants included in the analysis for NDI were included, only patients evaluated using BSID-II were included in the analyses for MDI and PDI. A few outliers were moved back to an extreme quantile of the distribution to lessen their erroneous influence (winsorization). An odds-ratio, calculated from a logistic regression model (for the outcome NDI), or a beta coefficient (slope) of a linear regression model (for the outcomes MDI and PDI), were used to describe associations with growth parameters. The odds ratio is to be regarded as a ratio of the odds of being diagnosed with NDI, and the beta coefficient is to be interpreted as an average increase in the outcome, corresponding to a one-unit rise in the growth parameter. We included a random "centre effect" to all models in order to account for a potential clustering effect, producing (generalised) linear mixed models.

We also conducted adjusted analyses, including nine known risk factors for neurodevelopmental impairment in our models as available from the database (gestational age, sex, multiple birth, bronchopulmonary dysplasia, sepsis, necrotizing enterocolitis, retinopathy of prematurity, socioeconomic status, and major brain lesion), yielding adjusted odds ratios and adjusted beta values, to investigate whether the investigated associations could be the result of some confounding factors.

We pre-specified applying a Bonferroni correction to address multiple testing concerns, which resulted in p-values below 0.04/23=0.001 being considered significant. The glmer procedure from the lme4 package, which is available in the free statistical programme R, was used to calculate each of our models.

Results

These 250 were suitable for further analysis since 84.3% had a documented neurodevelopmental assessment at FU1 (BSID-II, n=113; Bayley III, n=76; GSID, n=51; just neurological exam, n=10; Figure 2). At birth and FU1, 11.2% and 11.8%,

respectively, of the infants included had weights below the 10th percentile.

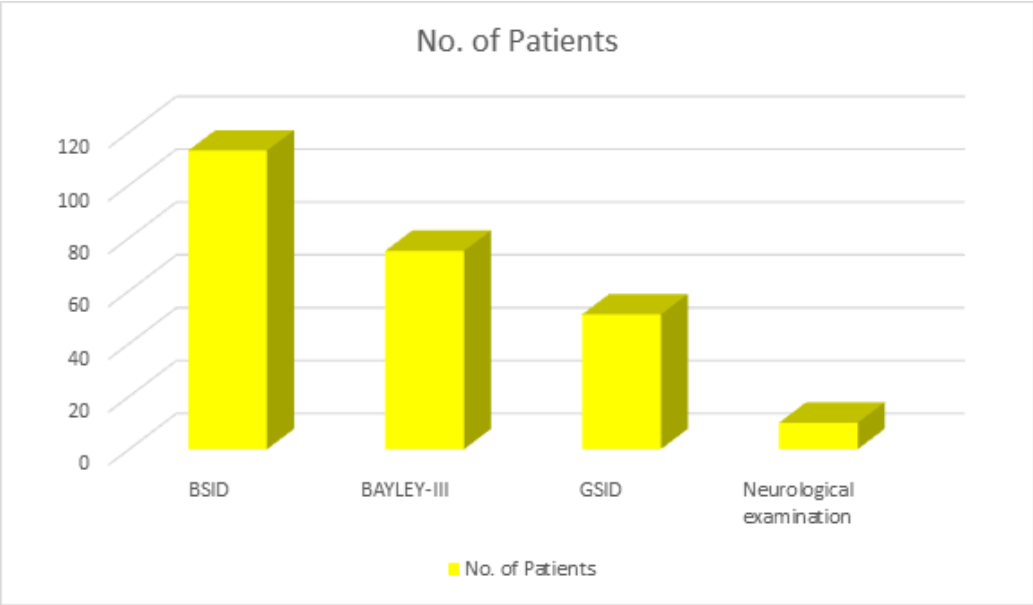

Figure 2: Neurodevelopmental assessment at follow up- 1-year

Infants who were included had lower mean (SD) GA (25.3 weeks (1.1) vs. 26.5 weeks (±1.1), p=0.013; lower mean birth weight (845 g (±187) vs. 887 g (±184), p=0.005; and longer duration of supplementary oxygen (43.4 days (±33.0) vs. 37.2 days (±33.1), p=0.014) than infants who were not assessed for FU2. Other perinatal and neonatal baseline factors (antenatal corticosteroids multiple birth, sex, prevalence of bronchopulmonary dysplasia, rate of retinopathy of prematurity, major brain lesions, sepsis, patent ductus arteriosus, duration of hospitalisation, and parental SES) did not differ between groups with and without FU1.

23.1% of all infants who underwent testing at FU1 had moderate to severe NDI. The mean (±SD) MDI and PDI of the infants who underwent the BSID-II testing were 88.8 (±18.1) and 86.8 (±17.6), respectively. The mean scores for the Bayley-cognitive III's and motor composites among the minority of infants who underwent additional testing were 99.0 (±38.0) and 96.3 (±36.6), respectively. The GSID's overall rating was 83.5 (±24.7). Participants' average body weights at birth, hospital discharge, and FU1 were 852g (1±88g), 2548g (±83g), and 10471g (±164g). The corresponding weight z-scores were correspondingly 0.11 (±0.87), 1.17 (±1.0), and 0.27 (±1.15).

Birth, discharge, and FU1 all had body length z-scores of 0.11 (±0.87), 1.28 (±1.41), and 0.34 (±1.23), respectively. Over the monitoring period, the head circumference z-score declined, with the lowest values occurring at FU1.

According to the predetermined threshold of significance, both unadjusted and adjusted regression analyses failed to find any statistically significant correlations between growth from birth to FU1 and neurodevelopment at FU1 (p 0.001). None of the three development outcome parameters (NDI, MDI, and PDI) or any of the four growth parameters were significantly correlated with one another (Table 1).

Table 1: Growth between birth and hospital discharge (delta1) and between birth and FU1 (delta2) with neurodevelopmental damage at 19 to 25 months corrected age, both unadjusted and adjusted

Criteria	Unadjusted regression		Adjusted regression	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Delta 1 weight z-score	0.91 [0.73,1.11]	0.2962	0.94 [0.76, 1.16]	0.6414
Delta 1 length z-score	0.98 [0.83, 1.17]	0.9251	1.01 [0.82, 1.20]	0.9775
Delta 1 HC z-score	1.01 [0.85, 1.20]	0.7891	1.00 [0.83, 1.20]	0.9264
Delta 1 BMI z-score	1.12 [0.97,1.31]	0.0841	1.03 [0.88, 1.20]	0.6205
Delta2 weight z-score	0.83 [0.73, 0.95]	0.0082	0.82 [0.71, 0.94]	0.0068
Delta2 length z-score	0.95 [0.84, 1.06]	0.4470	0.93 [0.82, 1.05]	0.3128
Delta2 HC z-score	0.92 [0.82-1.03]	0.1912	0.94 [0.84, 1.06]	0.4136
Delta2 BMI z-score	0.92 [0.83,1.02]	0.1544	0.91 [0.80,1.00]	0.0722

Neurodevelopment at FU1 was not significantly correlated with growth between birth and hospital release. No significant correlations between any of the four growth characteristics and neurodevelopmental parameters were found in the secondary analysis, as they weren't in the initial ones (Table 1).

35 analyses were conducted post hoc to examine the relationships between the three neurodevelopment outcomes and the four anthropometric parameters evaluated at three different time intervals. Eight of these had significant connections in the studies that were corrected. More specifically, significant correlations between weight and length at FU1 with moderate to severe NDI and length at birth and head circumference at FU1 with MDI were found (p=0.0003 and p=0.0006, respectively). Moreover, there were significant correlations between PDI and weight, length, and BMI at FU1 (p=0.0002, p=0.0018, p=0.0002, and p=0.0001, respectively), as well as length and head circumference at birth.

Independent analyses of patients with and without SGA were also conducted, and they largely failed to find any significant relationships between growth metrics and development. In particular, NDI did not significantly correlate with any of the eight growth indices studied. However, in both unadjusted and adjusted analyses for SGA patients, the weight z-score difference between birth and hospital discharge was substantially linked with MDI (p=0.0003 and p=0.0002). Moreover, in both unadjusted and adjusted analyses, the difference in weight and BMI z-scores between birth and FU1 was significantly linked with PDI (weight, p=0.0002 and p<0.0002; BMI, p=0.0003 and p<0.0001). In every one of these investigations, more growth was linked to greater development.

Discussion

Analysis of this population-based cohort of babies who were born extremely preterm did not reveal any statistical support for the association between 1-year neurodevelopmental outcomes and either growth between birth and discharge or growth between birth and age one.

Many studies have been conducted over the past few decades [9] on the relationship between postnatal growth and neurodevelopment in preterm newborns. The investigated patient group, sample size, primary outcomes, assessment measures, and confounding variable adjustment all exhibit significant heterogeneity, though. For instance, included patients were divided into groups according to whether they were tiny for gestational age or adequate for gestational age, and growth was divided into groups based on the quartiles of the normative values of the patient group as a whole [10].

Overall, the majority of papers suggest a connection between postnatal growth and neurodevelopment, but most of them have some significant shortcomings. Just a small number of studies specifically corrected development for socioeconomic status, a crucial predictor of neurodevelopment [11].

The French EPIPAGE study showed that preterm infants born at 32 weeks who were born small for gestational age had an elevated risk of cognitive impairment and inattention-hyperactivity at age 5. Moreover, cerebral palsy and academic difficulties were linked to kids with birthweights suitable for gestational age who had delayed postnatal growth [12].

Moreover, growth and development in a group of Brazilian children with very low birthweights (birthweight 1500 g) were evaluated. This investigation demonstrated that growth was not a significant predictor of neurodevelopment, which is consistent with our findings [13].

Three growth indices in the SGA infants of the current study were linked to neurodevelopment, according to post hoc analyses. Only SGA patients had these connections found; neither non-SGA patients nor the overall patient population did. Future research may therefore concentrate specifically on SGA patients.

It is significant to note that intrauterine growth was not considered a risk factor in this study, despite the fact that numerous studies have shown that intrauterine growth restriction is linked to impaired development [14, 15]. Improving preterm infants' growth in recent years has been a major goal in neonatology in order to promote optimal development. The findings of our study raise the question of whether promoting weight gain helps preterm infants' neurodevelopment. In addition, numerous studies have shown a link between postnatal weight gain and obesity, insulin resistance, and elevated blood pressure [16].

Therefore, it is necessary to weigh the risks associated with increased weight gain against any potential benefits. In actuality, contemporary nutritional techniques attempt to maximize the quantity and quality of the food, boost breast milk consumption, and to duplicate body composition as closely as feasible to that of term newborns. There are still many unanswered questions about optimal growth. [17] In particular, nutritional status in preterm infants is very complex, and measuring growth in grams and centimeters describes growth only quantitatively, but not qualitatively. Micronutrient availability or the measurement of lean body mass may provide additional insight into the best conditions for growth.

Conclusion

According to the current study's findings, neither growth between birth and hospital discharge nor growth between birth and one year of age was linked to impaired neurodevelopment in this cohort of extremely preterm babies. It may be less important than previously thought that postnatal growth serves as a predictor of the neurodevelopmental outcome during infancy.

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