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REGULAR ARTICLE

Twelve-month neurodevelopmental outcome in preterm infants with and without intrauterine growth restriction

Nelly Padilla (fpadilla@clinic.ub.es)[1,2,3], Josep Perapoch[3], Antonio Carrascosa[2,4], Ruthy Acosta-Rojas[1,2], Francesc Botet[5], Eduard Gratacós[1,2,3]

1.Department of Maternal-Fetal Medicine, ICGON, Hospital Clinic-IDIBAPS, Universidad de Barcelona, Barcelona, Spain
2.Center for Biomedical Network Research on Rare Diseases (CIBERER), Instituto de Salud Carlos III, Barcelona, Spain
3.Department of Obstetrics and Neonatology, Hospital Vall d'Hebron, Universidad Autónoma de Barcelona, Barcelona, Spain
4.Department of Pediatrics, Hospital Vall d'Hebron, Universidad Autónoma de Barcelona, Barcelona, Spain
5.Department of Neonatology, ICGON, Hospital Clinic-IDIBAPS, Universidad de Barcelona, Barcelona, Spain

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Correspondence
Nelly Padilla, Fetal Medicine Research Group – Department of Maternal Fetal medicine, ICGON, Hospital Clínic. Sabino de Arana 1, 08028 Barcelona, Spain.
Tel: +34 93 227 9333 |
Fax: +34 93 227 9336 |
Email: fpadilla@clinic.ub.es

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ABSTRACT

Aim: To evaluate the neurodevelopmental outcome at 12 months' corrected age in preterm infants with and without severe intrauterine growth restriction.

Methods: This prospective follow-up study included 37 infants with severe intrauterine growth restriction and 36 appropriate-for-gestational-age infants born between 26 and 34 weeks. Neonatal and infant data were prospectively recorded. Infants were assessed at 12 ± 2 months' corrected age with the Hammersmith Infant Neurological Examination and the Bayley Scale for Infant Development version-II.

Results: Both groups were similar in demographic characteristics and perinatal status. No significant differences in neurodevelopmental performance were found. The mental development index was 98.8 (SD 9.0) vs 98.4 (SD 13.1) ($p = 0.9$) and the psychomotor development index was 91.7 (SD 9.9) vs 95.5 (SD 13.4) ($p = 0.2$) for the study and reference groups respectively. Neurological assessment showed no significant differences between the two groups.

Conclusion: Although the study group showed a non-significant trend towards a lower score in the psychomotor development index than the reference group, significant differences at 12 months could not be demonstrated. IUGR infants continued to have significantly lower weight, length and head circumference at 1 year.

INTRODUCTION

Preterm newborns are at high risk for brain damage. Approximately 5–7% of preterm neonates are born with intrauterine growth restriction (IUGR), which poses an increased risk for an adverse neurodevelopmental outcome (1,2). Recent long-term postnatal studies in children with IUGR have described a higher prevalence of developmental deficits specifically related to cognitive functions involving poor academic performance, memory, visuomotor and language difficulties and executive function problems (3,4).

Recent advanced magnetic resonance imaging studies have shown that IUGR is associated with structural differences that can be identified very early in life. Studies in preterm newborns with IUGR evaluated at term-corrected age have found reductions in the cerebral cortical grey matter (5), hippocampal volume (6) and sulcation index (7), which were accompanied by less mature behavioural scores. These macrostructural alterations have been associated with microstructural and metabolic changes assessed by diffusion tensor imaging and spectroscopy (8), which could underlie the increased risk of neurodevelopmental deficits. In addition, correlations between growth patterns and neurocognitive development in IUGR infants have been demonstrated (9).

Neurodevelopmental problems in preterm IUGR infants should ideally be identified as early in life as possible to establish early intervention strategies. However, diagnosis of neurodevelopmental deficits very early in life remains elusive. The results of developmental studies in the first few years of life using either Griffith's scale (10) or the Bayley Scale of Infant Development version II (BSID-II) (6,11) have failed to show clear differences in comparison with preterm children with normal birth weight. Among the reasons proposed to explain the absence of differences are the

Abbreviations
AGA, appropriate for gestational age; BSID-II, Bayley Scale for Infant Development version II; CI, cephalization index; CRIB, Clinical Risk Index for Babies; GA, gestational age; HC, head circumference; HINE, Hammersmith Infant Neurologic Examination; IUGR, intrauterine growth restriction; MDI, Mental Developmental Index; NICU, neonatal intensive care unit; PDI, Psychomotor Developmental Index.

timing of assessment, which might be too early to detect neurodevelopmental changes, and the poor sensitivity of the available tests to assess cognitive performance (2). However, another potential source of confusion is the wide variability in the definition of IUGR in published studies, which can range from foetuses with early-onset growth restriction to mild forms of small-for-gestational-age foetuses, a diagnostic category containing a substantial proportion of constitutionally small foetuses without true growth restriction (12). We hypothesized that better prenatal characterization and selection of severely affected infants might help to identify differences between preterm infants with and without IUGR. The aim of this study was to evaluate neurodevelopmental outcome in a cohort of well-defined early-onset severe IUGR infants and to compare their performance with appropriate-for-gestational-age (AGA) preterm infants at 12 months' corrected age. We also documented the growth parameters pattern of both groups.

PATIENTS AND METHODS

This sample was drawn from a cohort of mothers and their newborns participating in a prospective study designed to elucidate the impact of prenatal intrauterine growth restriction exposure on brain development and its developmental consequences in foetuses and children. The infants were selected from the preterm population born at the Vall de Hebron Hospital (Barcelona, Spain) between 2005 and 2006, including a consecutive sample of 45 singleton premature infants with a prenatal diagnosis of IUGR established before 34 weeks of gestation and 46 AGA infants matched in the neonatal intensive care unit (NICU) for gender and gestational age (GA) (±2 weeks) at delivery. All cases and controls underwent routine foetal ultrasound. In all patients, enrolled pregnancy was dated on the basis of a first-trimester ultrasound and the presence of normal or abnormal growth was determined always in relation with the estimation of GA on the basis of first-trimester ultrasound. IUGR was defined as an ultrasound-estimated foetal weight below the 10th centile for GA confirmed at birth, together with an abnormal blood flow in the umbilical artery (pulsatility index >2 standard deviations for GA.

Infants with chromosomal, genetic or structural defects and signs of intrauterine infection or neonatal early-onset sepsis as defined by positive blood culture within the first 72 h of life were not eligible for this study. The study protocol was approved by the local Ethics Committee and written informed consent was obtained from the parents or legal guardians of all participants.

Prenatal and neonatal data were prospectively recorded, including GA, weight, length, head circumference (HC), length of stay in the NICU, Clinical Risk Index for Babies (CRIB), use of antenatal steroids and neonatal death. Respiratory, cardiovascular, gastrointestinal, metabolic, infectious morbidity and neonatal ultrasound findings were included. Local reference standards were used (13,14).

Follow-up

Infants were assessed at 12 ± 2 months' corrected age. The Hammersmith Infant Neurologic Examination (HINE) was performed (15). At 12 months, a global score equal to or above 73 is considered as optimal. Cognitive and psychomotor development was assessed using the BSID-II. The Mental Development Index (MDI) assesses environmental responsiveness and sensorial and perceptual abilities, while the Psychomotor Development Index (PDI) assesses gross and fine motor skills. The BSID-II has a mean value of 100 with a SD of 15. All neurological and developmental examinations were performed by a single, trained, examiner with previous experience with the HINE and BSID-II. The examiner was not informed about the infant's medical history. Data on breastfeeding, hospitalization in the first year of life, sleeping and eating, use of early intervention services, attendance at day care center and maternal education were recorded using a questionnaire at assessment.

Anthropometric data were collected. Length was measured in supine position with straight back and knee on a standardized infantometer. Weight was measured with the infants undressed on a calibrated infants' balance scale. The maximum occipital–frontal HC was measured using a standard paper tape, taking the largest measurement across the occipital frontal line. An average value of three measurements was recorded.

Anthropometric measurements were converted to Z-scores relative to local growth reference standards. Suboptimal catch-up growth in weight, length and HC was defined as a Z-score of the corresponding measurement of <–2 SDs for age and gender.

As the infants included in the study group had late-diagnosis of IUGR, the brain-sparing effect described in these infants results in a high brain body ratio. The cephalization index (CI) (neonatal head circumference $\times 10^2$/birth weight) (16) was calculated to reflect the severity of IUGR and the brain-sparing process.

Statistical analysis

The sample size was calculated on the basis of the estimated differences in PDI between study groups. In a previous study comparing premature with normal infants, the PDI within each study group was normally distributed with a SD of 6.7 (17). In order to observe a difference between means in the experimental and control groups of 4 units, a minimum sample size of 35 would allow to reject the null hypothesis with a probability (power) 72% and a type I error probability of 0.05. In order to compensate for the rate of cases lost to follow up, the study design contemplated enrolment of a minimal number of 45 cases and controls and the inclusion period was closed when this number was achieved in both groups (the control group finally included 46 patients). Comparisons between groups were carried out using the two-sided Mann–Whitney *U*-test, *t*-test or Fisher's exact test depending on the variables. Neurobehavioural outcome was controlled for confounders such as maternal education and use of early intervention service by multiple lineal or logistic regression. Bivariate correlation between

BSID-II scores and neonatal paramenters were assessed by Pearson correlation. Differences were considered significant when p values were <0.05. All statistical analyses were calculated using the SPSS 13.0 (SPSS for Windows, SPSS Inc, Chicago, IL, USA) statistical software.

RESULTS

Forty-five and 46 infants were initially included for follow-up. Three of 40 (7.5%) IUGR infants and nine of 45 (20%) preterm controls were lost to follow-up due to the parents' refusal to continue participation in the study protocol. Thus, the final study sample included 37 IUGR and 36 AGA infants. There were no differences between the lost-to-follow-up group and study infants in perinatal or demographic characteristics except for the CRIB score, which was lower in the lost-to-follow-up group [3.6 (SD 1.5) vs 7.0 (SD 2.4), p = 0.03)]. None of the study or control group infants died during the follow-up period. Both groups were similar in demographic characteristics and perinatal status as shown by the CRIB score (Table 1). There were no significant differences in neonatal morbidity except for an increase prevalence of transient periventricular echodensities and periventricular leukomalacia grade I in the IUGR group (18/45 and 8/46, p = 0.02 and 7/43 and 1/45, p = 0.02 respectively). Concerning nutritional management in NICU, neonates in the two study groups had essentially equivalent nutritional intakes.

The biometric parameters of the study groups are summarized in Table 2. Between birth and 12 months of age, the mean value of the HC in the IUGR group decreased compared with that in AGA infants, although this difference did not reach statistical significance. However, the IUGR infants developed microcephaly in a significant proportion compared with AGA group [15/38 (39.5%) vs 7/39 (17.9%), p = 0.046 respectively]. The proportion of infants with suboptimal catch-up growth in one or more biometric parameters was high in IUGR infants [16/37 (43.2%) vs 8/36 (22.2%); p = 0.08]. No statistically significant differences were observed between IUGR and AGA groups in the clinical follow-up during the first year of life. Neurological assessment showed no significant differences between the two groups [74.6 (5.9) in IUGR and 74.9 (3.2) in AGA infants].

There were no significant differences in mean MDI and PDI scores between both groups (Table 3). The study group showed a non-significant trend towards a lower score in the PDI than the reference group. There were no significant differences between the IUGR and AGA groups in the proportion of infants with cut-off BSID-II scores below 85. In the whole sample, there were significant correlations between BSID-II scores and neonatal parameters except for HC, which showed a trend towards significance (Table 4). In IUGR infants, we found a significant positive correlation between MDI and the value of HC on discharge from NICU (r = 0.450, p = 0.01). In the AGA group, no significant correlations were demonstrated.

DISCUSSION

The results of this study show that, contrary to the study hypothesis, there are no significant differences in severe

Table 1 Characteristics of the study groups

Perinatal characteristics	IUGR(n = 45)	AGA (n = 46)	p value
Gestational age (weeks + day)*	30 + 3 (27 + 3–33 + 3)	30 + 1 (26 + 2–34 + 1)	ns
Gender (male), n (%)†	29 (64.4)	29 (63.0)	ns
Mode of delivery (cesarian section), n (%)†	41 (91.1)	38 (82.6)	ns
Umbilical artery pH‡	7.24 (0.09)	7.28 (0.1)	ns
Apgar score 5 min*	8 (7–9)	9 (8–10)	ns
Stay in NICU (days)*	30 (15–65)	28 (5–62)	ns
Postmenstrual age at discharge from NICU*	36.5 (31.4–40.5)	34.3 (30.2–42.3)	0.004
Clinical Risk Index for Babies*	7 (2–15)	8 (1–14)	ns
Prenatal steroids, n (%)†	34 (75.5)	28 (60.8)	ns
Neonatal death, n (%)†	5 (11.1)	1 (2.2)	ns
Demographic characteristics			
Non-white ethnicity n (%)†	5/45 (11.1)	4/46 (8.7)	ns
Breastfeeding duration, n (%)†			
Never	5/33 (13.2)	4/35 (10.3)	ns
≤4 months	3/35 (7.9)	3/36 (7.7)	ns
≥4 months	30/38 (78.9)	32/39 (82.1)	ns
Maternal age‡	31.5 (5.0)	31.7 (5.6)	ns
Use of early intervention services†	17/38 (44.7)	11/39 (28.2)	ns
Maternal education†			
High	30/45 (66.7)	24/45 (52.2)	ns
Intermediate	12/45 (26.7)	20/45 (43.5)	ns
Low	3/45 (6.7)	2/46 (4.3)	ns

IUGR = Intrauterine growth restriction; AGA = Appropriate for gestational age; NICU = Neonatal intensive care unit; ns = Non-significant.
*Mann–Withney *U*-test, data presented as median (range).
†Fisher exact test, data presented as n (%); ‡*t*-test; data presented as mean ± SD.

Table 2 Anthropometry of the study groups*

Biometric parameters	IUGR infants (n = 45)	AGA infants (n = 46)	p value
Birth			
Birthweight (g)	981.2 (375.1)	1367.6 (445.7)	0.000
Z-score	−2.67	0.33	0.000
Length (cm)	35.8 (4.55)	39.6 (3.71)	0.000
Z-score	−2.63	0.24	0.000
Head circumference (cm)	27.8 (3.89)	27.2 (3.47)	ns
Z-score	−0.87	−0.62	ns
Cephalization index (CI) ($cm \times 10^2/g$)	2.80 (0.62)	2.14 (0.48)	0.000
CI median (minimum–maximum)	2.81 (1.56–4.38)	2.08 (1.33–3.38)	0.000
Discharge from the NICU	n = 40	n = 45	
Weight (g)	2109 (420.60)	2157 (333.70)	ns
Z-score	−1.41	−0.34	0.003
Lenght (cm)	43.7 (2.71)	44.7 (2.86)	0.14
Z-score	−1.79	1.94	0.002
Head circumference (cm)	32.6 (1.37)	32.0 (1.67)	ns
Z-score	−0.25	−0.14	ns
1-year	(n = 38)	(n = 39)	
Weight (kg)	8.43 (1.16)	9.68 (1.50)	0.001
Z-score	−1.34	−0.19	0.001
Height (cm)	72.16 (4.36)	76.0 (4.97)	0.001
Z-score	−1.26	0.31	0.001
Head circumference (cm)	45.33 (1.77)	46.16 (1.83)	ns
Z-score	−1.34	−0.46	0.01

IUGR = Intrauterine growth restriction; AGA = Appropriate for gestational age; NICU = Neonatal intensive care unit.
*t-test; data presented as mean ± SD.

Table 3 Twelve-month developmental assessment

Index	IUGR infants (n = 37)	AGA infants (n = 36)	p value
MDI*	98.8 (9.0)	98.4 (13.1)	ns
PDI*	91.7 (9.9)	95.5 (13.4)	ns
PDI < 85, n (%)†	1 (2.7)	3 (8.3)	ns
MDI < 85, n (%)†	7 (18.9)	6 (16.7)	ns

IUGR = intrauterine growth restriction; AGA = appropriate for gestational age; MDI = Mental Developmental Index; PDI = Psychomotor Developmental Index.
*Data presented as mean ± SD.
†Data presented as n (%).

Table 4 Developmental correlations with neonatal data for the whole sample (N = 77)

Anthropometric data	MDI, r (p)	PDI, r (p)
Birthweight	0.249 (0.034)	0.279 (0.017)
Length at birth	0.211 (0.073)	0.350 (0.002)
Head circumference at birth	0.230 (0.050)	0.210 (0.069)
Gestational age	0.353 (0.002)	0.231 (0.049)
Cephalization index	−0.143 (0.232)	−0.321 (0.006)
Weight (12 months)	0.135 (0.259)	0.202 (0.109)
Height (12 months)	0.215 (0.070)	0.276 (0.022)
Head circumference (12 months)	0.159 (0.191)	0.187 (0.124)

MDI = mental development index; PDI = psychomotor development index.

IUGR infants in neurological and developmental outcome when compared with preterm AGA infants at 12 months' corrected age. However, IUGR infants have significantly lower weight, length and head circumference.

Our findings are in line with those of Wocadlo and Rieger (11) who reported no differences in 19 preterm small-for-gestational-age and 19 AGA infants using the BSID-II and Griffiths' mental development scales at 12 months. However, it is likely that the authors studied a less severely affected population than that analyzed in this study. Thus, in the study (11), small-for-gestational-age was defined as a birth weight below the 10th percentile, but the observation of an abnormal umbilical artery Doppler was not a requirement. In another study, Gortner et al. (10) evaluated 74 children with a birth weight below the 10th percentile at 22 months with the Griffiths scale and reported no significant differences in neurodevelopmental outcome. Finally, using a definition of IUGR similar to that used in this study, Lodygensky et al. (6) assessed the development of 13 growth restricted and 13 appropriate preterm infants at 24 months using the BSID-II and found no statistical differences between groups. Regarding neurological assessment our results are in line with those of Karagianni et al.(18) who investigated the neurological outcome of premature small-for-gestational-age and normally grown infants. While the small-for-gestational-age group scored lower than controls, median global scores in both groups were within the optimal range.

Our results support the notion that current tests are unable to demonstrate neurodevelopmental differences in children with IUGR in the first years of life. The existence of such differences is strongly suggested by long-term longitudinal studies showing an increased rate of developmental disabilities in these children (3,4,9).

The failure to demonstrate neurodevelopmental differences at age 12 months in survivors of severe IUGR may indicate that the processes underlying perceptual, memory and executive function are subtle and cannot be captured by the BSID-II. At this age, most developmental capacities and cognitive processes begin to be established and become prominent later in childhood when their assessment allows probable differences to be identified (19). Another reason for the lack of differences could be related to increased sensorymotor stimulation in the NICU environment in both groups. This fact has been related to acceleration in the white matter maturation compared with born term neonates (20). This finding could play an important role in the first year of life.

We found a characteristic pattern of poor weight, length and HC gain in the first year of life in preterm IUGR infants. This is in line with other studies that have demonstrated growth impairment in IUGR infants (3,9). As both groups were comparable in neonatal morbidity and NICU nutritional management, poor growth in IUGR group could not be the consequence of previous neonatal complications. Therefore, nutritional, environmental and genetic factors should be considered (21). In this manner, improvements on nutritional management after discharge may have some effects on the postnatal growth in IUGR infants.

Infants in both groups had adverse influences at a critical period of brain growth that can be seen at 12 months when microcephaly appears in a large proportion of IUGR infants, suggesting greater vulnerability in brain growth compared with AGA infants. As mental outcome in the first years appears to be closely related to growth (22) and brain volume, Tan L et al. (23) suggest that improving nutrition in very preterm infants may improve brain growth and maturation. Specifically in IUGR children, the correlation between the CI (3) and somatic growth (9) indices are clearly associated with outcome at 10 years of life. Although no differences in neurodevelopmental scores were demonstrated at 1 year, we found a significant correlation between MDI and HC at discharge, which points the necessity of later developmental evaluations when differences between groups could be evident.

The most important strength of the current study is that the study group was well characterized according to prenatal features. IUGR was diagnosed according to specific criteria for growth restriction, which requires the observation of Doppler measurements indicative of placental insufficiency. In addition, both groups were similar in GA at delivery and neonatal morbidity. This study has some limitations. First, the relatively small sample may have prevented statistical differences from being observed in some comparisons. Second, the AGA preterm group cannot be considered as a normal population due to the strong influence of prematurity and its known effects on normal brain development. Third, only one developmental evaluation was performed in each infant and assessment at multiple developmental time points would have strengthened the conclusions. Finally, the lack of information about nonformula foods that infants received during the first year of life.

In conclusion, this study failed to demonstrate neurodevelopmental differences in premature infants with and without severe IUGR assessed with the BSID-II. However, we found that IUGR infants lag behind AGA infants in their growth parameters at first year of life. As we detected lower catch-up growth in IUGR infants and the relationship of these parameters with neurodevelopment is clear, studies involving more infants, more sensitive tools and nutritional management are warranted.

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