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Neurodevelopmental assessment of very low birth weight preterm infants at corrected age of 18-24 months by Bayley III scales

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Abstract

Objective: To evaluate the prevalence of delay and factors associated with neurodevelopmental scores in premature infants.

Methods: Cross-sectional study to assess the development by Bayley Scales III, including very low birth weight preterm infants aged 18 to 24 months who were under follow-up at the outpatient clinic for preterm infants. Congenital malformation, genetic syndrome, symptomatic congenital infection at birth, deafness, and blindness were excluded. Numerical variables were compared by Mann-Whitney or Student *t* test and categorical variables by chi-square or Fisher's exact test. Factors associated with developmental scores were analyzed by linear regression, and statistical significance level was established at $p < 0.05$.

Results: Out of the 58 children included, four (6.9%) presented cognitive delay, four (6.9%) motor, 17 (29.3%) language, 16 (27.6%) social-emotional and 22 (37.0%) adaptive-behavior delay. By multiple linear regression, the variables: social classes CDE (-13.27; 95%CI: -21.23 to -5.31), oxygen dependency at 36 weeks of corrected age (-8.75; 95%CI: -17.10 to -0.39) decreased the cognitive developmental score. Periventricular leukomalacia decreased the cognitive (-15.21; 95%CI: -27.61 to -2.81), motor (-10.67; 95%CI: -19.74 to -1.59) and adaptive-behavior scores (-21.52; 95%CI: -35.60 to -7.44). The female sex was associated with higher motor (10.67; 95%CI: 2.77 to 12.97), language (15.74; 95%CI: 7.39 to 24.09) and social-emotional developmental scores (10.27; 95%CI: 1.08 to 19.46).

Conclusions: Very low birth weight preterm infants aged from 18 to 24 months of corrected age presented more frequently language, social-emotional and adaptive-behavior delays. The variables: social classes CDE, periventricular leukomalacia, bronchopulmonary dysplasia and male sex reduced the neurodevelopmental scores.

J Pediatr (Rio J). 2012;88(6):471-8: Infant premature, very low birth weight infant, child development.

Introduction

Prematurity is one of the leading causes of morbidity, mortality and neurodevelopmental disorders in children.¹⁻³ An early recognition of abnormal neurodevelopment

promotes including the child in specific intervention programs, minimizing the risks of irreversible dysfunctions and improving the quality of life.^{4,5}

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Among the instruments available to assess development, the Bayley Scales of Infant Development are the most commonly used in preterm infants.⁶ The two initial versions of the Bayley scales evaluate two development scores: mental, which includes cognitive and language assessment, and psychomotor development.⁷

The second version (Bayley II) was widely used in researches,⁸⁻¹⁰ but a limitation of this method is the fact that the cognitive component is assessed by the combined measure of cognition and language. This means that if the level of mental development is low in version II, it can represent a delay in language, or in the cognitive part, or in both. Thus, version III was developed in 2006 to separate the mental development index into cognitive abilities and language abilities, and to separate the psychomotor development index into gross and fine.^{6,7}

However, there are few studies using the Bayley III Scales in preterm infants at risk of neurodevelopment delay, especially in Brazil.¹¹

In this context, the objectives of this study were to assess the prevalence of delays in the development of cognitive, motor, language, and adaptive behavior skills in very low birth weight infants and to identify the factors associated to the variation in the development scores.

Methods

It was a cross-sectional study performed at the Preterm Outpatient Clinic within Universidade Federal de São Paulo Medical School. This project was approved by the Research Ethics Committee of the institution, and informed consent was obtained from parents.

The study included children at corrected age of 18-24 months, born with gestational age below 37 weeks and weight lower than 1,500 g, under outpatient follow up at the Preterm Outpatient Clinic of the institution. The exclusion criteria were: congenital malformation, genetic syndrome, symptomatic congenital infection at birth, deafness, and blindness.

We collected maternal, neonatal, and postnatal demographic and clinical characteristics, by consulting the medical records of the child during hospitalization in the neonatal unit and outpatient follow up, besides interview with parents.

Peri-intraventricular hemorrhage and periventricular leukomalacia were diagnosed by serial cranial ultrasound, according to routine practice at the institution: first exam between 4-7 days of life, second between 10-14, and third with 30 days of life. Moreover, in newborns with birth weight < 1,000 g, magnetic resonance imaging was performed. For peri-intraventricular hemorrhage, we used the criteria of Papile et al.¹² For the diagnosis of leukomalacia, we considered white matter cystic or focal lesions, images of diffuse echodensity persisting for

more than 2 weeks or diagnosis by magnetic resonance imaging.^{13,14}

Clinical sepsis was considered in the presence of clinical signs of infection and need for antibiotics, with or without positive blood culture.^{15,16}

Regarding bronchopulmonary dysplasia, it was defined as oxygen dependence at 36 weeks of corrected gestational age.¹⁷

To evaluate development, we used Bayley scales of Infant Development III,⁶ always administered by the same researcher, in a calm environment.

To characterize development, two categories were defined for each of the five Bayley III subscales:

- Normal: composite score equal to or greater than 85 (normal or accelerated development).
- Abnormal: composite score lower than 85 (mild, moderate or significantly delayed development).

So as not to interfere in the evaluation of the scales of development, the collection of demographic and clinical data was performed after the administration of the scales.

Numerical variables were expressed as median (variation) and compared by the Mann-Whitney test, or as mean and standard deviation and compared by Student *t* test. Categorical variables were expressed in number and percentage and compared by the chi-square or Fisher's exact test. Factors associated with development scores were examined by univariate and multiple linear regression analysis. The univariate analysis included factors that, from the clinic point of view, could influence the development scores. The multiple linear regression analysis included up to five variables in each model, according to their clinical and/or statistical significance ($p < 0.2$).

Statistical analyses were performed in the SPSS software for Windows, version 17.0 (Chicago, IL, USA), and statistical significance level was established at 5%.

Results

Among the 177 children born from January 2007 to July 2008, it was not possible to locate the medical records of two (1.1%). Out of the 175 children identified, 66 (37.7%) progressed to death in the unit, and 109 (62.3%) were discharged. Among these, 25 (22.9%) parents chose not to attend the outpatient clinic. Out of 84 children enrolled, 18 (21.4%) abandoned the follow up before the study and one (1.2%) was excluded by congenital error of metabolism. Out of 65 children under follow up at the time, six (9.2%) were not included due to refusal of parents and one (1.5%) did not cooperate in the testing. Therefore, 58 (89.9%) eligible children were studied, who were effectively being monitored, which corresponded to 53.7% of the children who were discharged from the neonatal unit and met the inclusion criteria (Figure 1).

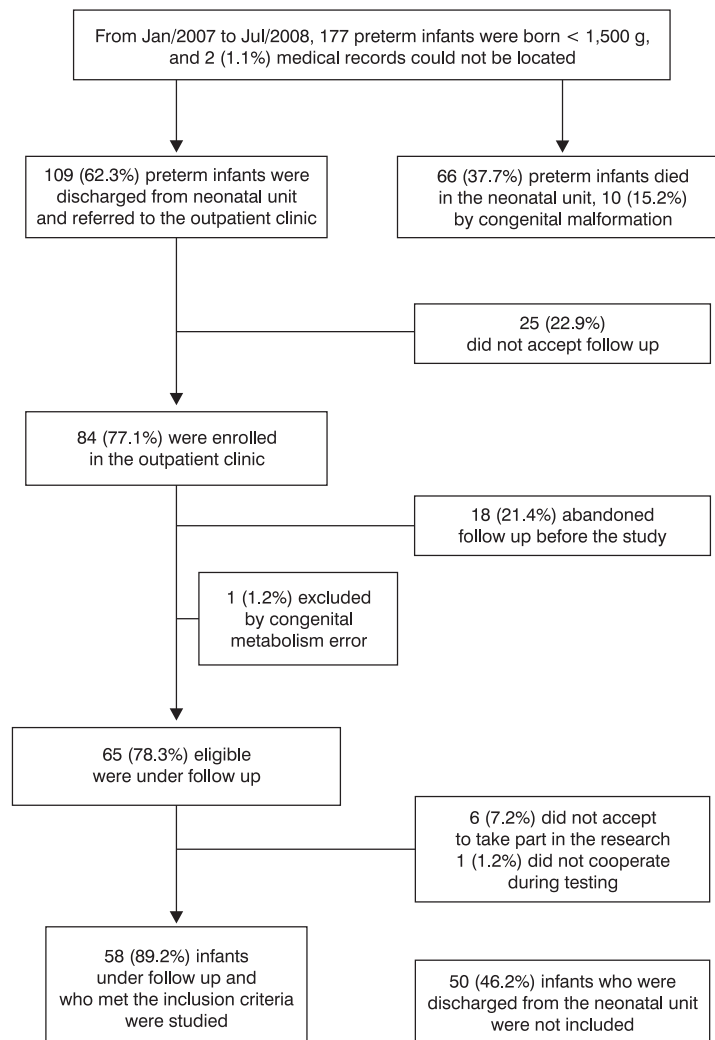


Figure 1 - Flowchart of preterm infants involved in the study

There was a comparative analysis between the preterm neonates included, and those who were not included in the study, in relation to the main maternal and neonatal variables that could influence the developmental scores (Table 1). We observed that both groups differed only in maternal age or in the use of antenatal corticosteroids. These two variables were then tested in the univariate regression model, showing that none of them were significant for any of the areas of development ($p > 0.2$).

Bayley scales were administered on average at corrected age of 20.6 ± 1.8 months, during 60 to 120 minutes.

Among the children assessed, four (6.9%) presented cognitive impairment; four (6.9%), motor; 17 (29.3%), language; 16 (27.6%), social-emotional; and 22 (37.9%), adaptive behavior.

Children with cognitive impairment presented lower Apgar scores at 1 minute (5.0 ± 1.8 vs. 7.3 ± 1.6 ; $p = 0.008$) and at 5 minutes (7.3 ± 1.5 vs. 8.8 ± 0.6 ; $p < 0.001$) and higher frequency of clinical sepsis (100 vs. 35.2%; $p = 0.021$), compared to those without cognitive impairment. In the presence of motor changes, lower Apgar scores at 5 minutes were observed (7.5 ± 1.5 vs. 8.7 ± 0.7 ; $p = 0.015$) and higher

Table 1 - Clinical and demographic characteristics of children eligible for the study, according to their inclusion or not in the research

Variables	Included (n = 58)	Not included (n = 50)	p
Maternal age (years)	30.0±7.9	26.0±6.0	0.001*
Pre-natal care - n (%)	53 (91.4%)	46 (92.0%)	0.635 [‡]
Pre-eclampsia - n (%)	25 (43.1%)	13 (26.0%)	0.063 [‡]
Chronic hypertension - n (%)	7 (12.1%)	9 (18.0%)	0.387 [‡]
Chorioamnionitis - n (%)	4 (6.9%)	5 (10.0%)	0.581 [‡]
Use of antenatal corticosteroids - n (%)	18 (31.0%)	27 (54.0%)	0.016 [‡]
Cesarean delivery - n (%)	42 (72.4%)	32 (64.0%)	0.348 [‡]
Female sex - n (%)	30 (51.7%)	27 (54.0%)	0.813 [‡]
Gestational Age (weeks)	30.0±2.5	29.0±3.2	0.752 [‡]
Birth weight (grams)	1,172±220	1,105±245	0.138*
1st minute Apgar	7.2±1.7	7.1±1.5	0.918*
1st minute Apgar < 7	15 (25.9%)	12 (24.0%)	0.824 [‡]
5th minute Apgar	8.7±0.8	8.7±0.6	0.534*
5th minute Apgar < 7	2 (3.4%)	0 (0%)	0.498 [§]
Small for gestational age - n (%)	21 (36.2%)	22 (44.0%)	0.409 [‡]
Respiratory distress syndrome - n (%)	33 (56.9%)	30 (60.0%)	0.744 [‡]
O ₂ requirement at 36 weeks - n (%)	13 (22.4%)	15 (30.0%)	0.370 [‡]
Clinical sepsis - n (%)	23 (39.7%)	27 (54.0%)	0.136 [‡]
Peri-intraventricular hemorrhage - n (%)	35 (60.3%)	29 (58.0%)	0.805 [‡]
Periventricular leukomalacia - n (%)	5 (8.6%)	2 (4.0%)	0.447 [§]
Retinopathy of prematurity - n (%)	15 (25.9%)	20 (40.0%)	0.118 [‡]
Need for mechanical ventilation - n (%)	34 (58.6%)	33 (60.0%)	0.431 [‡]
Days of mechanical ventilation	5±9	13±8	0.051 [†]
Use of post-natal corticosteroids - n (%)	3 (5.2%)	5 (10.0%)	0.467 [§]
Days of hospitalization in the neonatal unit	56±24	66±4	0.227 [†]
Small for gestational age term infant - n (%)	44 (75.9%)	37 (74.0%)	0.752 [‡]

O₂ = oxygen.* Student *t* Test.

† Mann-Whitney.

‡ Chi-square.

§ Fisher's exact test.

incidence of periventricular leukomalacia (40 vs. 3.8%; $p = 0.034$). Language disorder occurred more frequently in males (65.9 vs. 17.6%; $p = 0.001$), in children with peri-intraventricular hemorrhage (82.4 vs. 51.2%; $p = 0.027$) and with longer hospitalization (72±29 vs. 49±19 days; $p = 0.002$). Changes in adaptive behavior were more frequent in the presence of periventricular leukomalacia (18.2 vs. 2.8%; $p = 0.043$).

Among the 58 children, 31 (53.4%) presented abnormalities in some area of development, 16 (27.6%) only in one area, eight (13.8%) in two, five (8.6%) in three, one (1.7%) in four and one (1.7%) in the five areas.

The characteristics of children with neurodevelopmental abnormalities are presented in Table 2.

The median scores for development were 102.0, 100.0, 93.0, 95.0 and 90.5 for cognitive, motor, language,

social-emotional and adaptive behavior areas respectively. Median scores of children with abnormalities were lower, compared to those without abnormalities ($p < 0.001$): 75.0 and 105.0 (cognitive), 76.0 and 100.0 (motor), 76.0 and 100.0 (language), 80.0 and 100.0 (social-emotional) and 73.0 and 101.0 (adaptive behavior), respectively.

Multiple linear regression demonstrated that the variables:

- CDE socio-economic class (-13.27; 95%CI -21.23 to -5.31), periventricular leukomalacia (-15.21; 95%CI -27.61 to -2.81) and oxygen requirement at 36 weeks (-8.75; 95%CI -17.10 to -0.39) decreased the scores of cognitive development, controlled for sex, clinical sepsis and use of postnatal corticosteroids ($p < 0.001$).
- Female sex (7.88; 95%CI 2.77-12.97) increased and periventricular leukomalacia (-10.67; 95%CI -19.742 to

Table 2 - Characteristics of children with neurodevelopmental delays in the areas of cognitive, motor, language, social-emotional and adaptive behavior development, expressed as median (variation) or single frequency

Variables	Cognitive (n = 4)	Motor (n = 4)	Language (n = 17)	Social-emotional (n = 16)	Adaptive behavior (n = 22)
GA (weeks)	29.8 (24.6-34.3)	31.8 (24.6-33.6)	29.7 (24.6-33.6)	30.4 (24.5-34.4)	29.9 (24.6-33.6)
Female sex - n (%)	1 (25.0)	1 (25.0)	3 (17.6)	7 (43.7)	9 (40.9)
Apgar at 5 minutes < 7 - n (%)	2 (50.0)	2 (50.0)	1 (5.9)	0 (0.0)	1 (4.5)
Weight (g)	1,050 (585-1,275)	1,267 (585-1,395)	1,165 (585-1,435)	1,287 (585-1,410)	1,265 (585-1,480)
SGA - n (%)	1 (25.0)	1 (25.0)	2 (11.8)	4 (25.0)	6 (27.3)
RDS - n (%)	3 (75)	3 (75.0)	13 (76.5)	10 (62.5)	14 (63.6)
O ₂ requirement at 36 weeks - n (%)	2 (50.0)	1 (25.0)	5 (29.4)	3 (18.7)	4 (18.2)
Clinical sepsis n (%)	4 (100.0)	2 (50.0)	10 (58.8)	8 (50.0)	8 (36.4)
PIVH - n (%)	3 (75.0)	2 (50.0)	14 (82.3)	10 (62.5)	14 (63.6)
PVL - n (%)	1 (25.0)	2 (50.0)	2 (11.8)	3 (18.8)	4 (18.2)
Postnatal corticosteroids use - n (%)	0 (0.0)	0 (0.0)	1 (5.9)	1 (6.3)	1 (4.5)

GA = gestational age; O₂ = oxygen; PIVH = peri-intraventricular hemorrhage; PVL = periventricular leukomalacia; RDS = respiratory distress syndrome; SGA = small for gestational age.

-1.597) decreased motor development scores, adjusted for socio-economic status, clinical sepsis, and small for gestational age at term ($p = 0.001$).

- Female sex (15.74; 95%CI 7.39-24.09) increased the score of language development, controlled for socio-economic, clinical sepsis, peri-intraventricular hemorrhage, and oxygen requirement at 36 weeks ($p < 0.001$).
- Female sex (10.27; 95%CI 1.08-19.47) increased the score of social-emotional development, adjusted for periventricular leukomalacia ($p = 0.029$).
- Periventricular leukomalacia (-21.53; 95%CI -35.609 to -7.444) decreased the score of the adaptive behavior development, controlled for sex ($p = 0.002$).

Discussion

In the present study, the prevalence of abnormal development in the cognitive, motor, language, social-emotional and adaptive behavior areas was 6.9, 6.9, 29.3, 27.6 and 37.9%, respectively.

Belonging to CDE socio-economic class was associated with lower cognitive scores. Periventricular leukomalacia was associated with lower cognitive, motor and adaptive behavior scores. Bronchopulmonary dysplasia was associated with lower cognitive score. Female sex increased the scores of language and social-emotional development.

The frequencies of disorders were lower in the cognitive and motor areas and higher in language when compared to those reported by Anderson et al.,¹⁸ who found delays in 13.0, 16.0 and 21.0%, respectively, for cognitive, motor and language areas in extreme preterm newborns, at 2 years, assessed by Bayley III. The lower frequency of cognitive and motor abnormalities may be due to the lower gestational age and birth weight observed in the present study, besides lower frequency of bronchopulmonary dysplasia (22.4 vs. 48.0%) and of postnatal corticosteroids use (5.2 vs. 19.0%). On the other hand, the lower frequency of language delay may reflect a better level of education observed in that research.

The mean scores found in this study were 102 for cognitive, 100 for motor, 93 for language, 95 for social-emotional and 90.5 for adaptive behavior. We found only one study that assessed the social-emotional and adaptive behavior scores in preterm infants by Bayley III. Such study assessed 20 premature infants, observing mean scores of 90 and 93 in the development of social-emotional and adaptive behavior and of 96, 95, and 100 in the cognitive, motor and language areas.¹⁹

As for the cognitive, motor and language areas, Anderson et al. showed similar values to those found in the present study, except for the cognitive score, which was slightly lower (96.9 ± 13.6).¹⁸ Bode et al. found mean scores of 92 and 97, respectively, for cognitive and motor areas in extreme preterm infants at 2 years old, evaluated by Bayley

III.²⁰ The difference in birth weight and gestational age may have influenced the results in both studies. However, the higher prevalence of periventricular leukomalacia and peri-intraventricular hemorrhage found in the present study may have contributed to equal the motor development scores between the two studies.

A Brazilian study with very low birth weight preterm infants, assessed by Bayley II, showed frequency of Mental Development Index (MDI) < 85 in 24 (38.7%) children and Psychomotor Development Index (PDI) < 85 in 16 (25.8%) preterm infants at 22-24 months corrected age. Compared to this study, the difference between the deficit percentages can be attributed to the difference in the frequency of periventricular leukomalacia and in the method used for the evaluation of development.¹⁰

The structural differences between Bayley II and Bayley III make it difficult to compare the scores and the levels of delay obtained in the two methods. Maguire et al. found a frequency of delayed mental development of 21.3% and 31.6% of delayed motor development in a similar population, i.e., preterm newborns with gestational age below 32 weeks and with mean weight of 1,261 g, assessed by Bayley II, at 2 years.²¹

These studies suggest that Bayley III could underestimate the rates of delay.^{10,21} Likewise, recent studies showed that the cognitive score obtained in the application of Bayley III was significantly higher than MDI assessed by Bayley II in term and preterm infants.²² In order to interpret the differences between the two methods, Lowe et al.,²² using analysis of covariance, developed a mathematical formula to convert the Bayley III scores into Bayley II scores (Bayley III scores = $[0.59 \times \text{Bayley III}] + 52$).

On the other hand, Moore et al.⁷ showed that MDI scores (Bayley II) and cognitive and language scores (Bayley III) differed in a heterogeneous manner, according to the score values. Thus, for MDI > 85, the corresponding values of Bayley III were similar. However, for MDI scores < 70, the positive predictive value of Bayley III was 78%. Therefore, the authors proposed using a cutoff point of Bayley III lower than 80 to detect moderate/severe involvement with sensibility of 89% and specificity of 99%, compared to 58 and 100%, respectively, when the Bayley III cutoff point below 70 was adopted.

The comparison of the groups with and without abnormalities in the subscales of this research showed that Apgar scores at the 1st and 5th minute, urinary tract infection and sepsis were more frequent in children with cognitive impairment; however, such factors did not present statistical significant in the linear multiple regression.

Similar results regarding the presence of infection were found in the literature. Silveira & Procianny¹⁰ found no significant association between levels of cytokines interleukin (IL), IL-6, IL-8, IL-10, IL-1 β and tumour necrosis

factor alfa (TNF- α) in infants at risk of early sepsis and mental development deficit at 22-24 months corrected age, assessed by Bayley II. Schlapbach et al. evaluated the effect of sepsis with positive blood culture in 541 infants with less than 28 weeks, at 2 years old, by Bayley II. By multivariate analysis, the authors evaluated the neurological impairment (MDI or PDI < 70) or cerebral palsy prognosis. In this study, sepsis with positive blood culture increased the chance of cerebral palsy [odds ratio (OR) = 3.23 (95%CI 1.23-8.48); $p = 0.017$], with a tendency to greater chance of neurological changes [OR = 1.69 (95%CI 0.96-2.98); $p = 0.067$]. However, suspect of sepsis without positive blood culture was not associated with neurological deficits at 2 years.²³

Comparing groups with or without changes in development also showed higher frequency of periventricular leukomalacia in those with motor and adaptive-behavior abnormalities and of peri-intraventricular hemorrhage in children with language disorders. These factors were recognized as risk factors for neurodevelopmental delays in another study.²⁴

Analysis of factors associated with developmental scores has confirmed that periventricular leukomalacia decreased the scores of cognitive, motor and adaptive behavior development. Similarly, Vohr et al. observed that the peri-intraventricular hemorrhage levels 3/4 and periventricular leukomalacia represented factors associated with higher risk of neurodevelopmental changes,²⁵ similar to those observed in the study by Silveira & Procianny,¹⁰ in which periventricular leukomalacia increased the chance of lower psychomotor development in very low birth weight preterm infants.

In the present study, we observed that bronchopulmonary dysplasia was associated with lower cognitive development scores, what is consistent with the literature.²⁶ Another study assessed the effect of chronic pulmonary disease (oxygen requirement at 36 weeks) at 2 years, by Bayley II, in 915 infants born before 28 weeks of gestational age. In this study, the frequency of MDI < 55 was of 9, 12, and 18%, and of PDI < 55 was of 7, 10, and 20%, respectively, for infants without pulmonary disease, with pulmonary disease and without mechanical ventilation need, and with pulmonary disease plus mechanical ventilation need.²⁷

In our country, Martins et al.²⁸ assessed the psychomotor development by Bayley II in a sample of 152 very low birth weight infants, of which 13.2% presented bronchopulmonary dysplasia (oxygen requirement at 36 weeks). Such authors found a high incidence of motor impairment (PDI < 85) at 6 months old corrected both in children with dysplasia (95.0%) and in those who had no dysplasia (47.7%). The high frequency of neurological impairment has been attributed in part to the early evaluation before 2 years old.²⁹ In this study, logistic regression analysis adjusted for confounding factors showed a significant association

between dysplasia and changes in psychomotor development scores (OR = 3.98; 95%CI 1.04-15.1).²⁸

Being female increased the scores of motor and language development. Likewise, Romeo et al. observed higher MDI scores in late female preterm infants, compared to males, at 18 months, assessed by Bayley II.³⁰ Other studies also indicated the female sex as a protective factor in neurological development.^{25,31}

Belonging to CDE socio-economic class decreased the cognitive development score. In relation to cognitive development, environmental factors, especially low socio-economic status, are determining for these abnormalities, suggesting that, as these children grow, environmental factors become more important than biological factors.³² The study by Voss et al. showed that in extremely premature infants, factors associated with IQ deficits were less educated mothers (OR = 21.9; $p < 0.001$) and peri-intraventricular hemorrhage (OR = 6.9; $p < 0.005$).³³

The main limitation of this study was the high loss of follow-up of infants with inclusion criteria. However, the comparison between included and not included preterm infants showed that the two groups were similar in relation to the main risk factors for development, differing only in relation to maternal age and rate of use of antenatal corticosteroids.

The highest percentage of use of antenatal corticosteroids observed in infants who were not included may have contributed to lessen the severity of bronchopulmonary dysplasia in more mature preterm infants and decrease mortality in extreme preterm infants,³⁴ however, the frequency of bronchopulmonary dysplasia was similar in both groups (22.4 vs. 30.0%; $p = 0.370$) and, likewise, similar to those reported by the Grupo Colaborativo Neocosur (rede neonatal do cone sul) in very low weight preterm infants (24.0%).³⁵ In addition, maternal age and use of antenatal corticosteroids, when tested in univariate linear regression model, showed no statistical significance in all development scores ($p > 0.2$).

In post-hoc analysis, it was observed that for the sample size included and an alpha error of 5% for cognitive and motor delay, the absolute accuracy was 7%. For delays in language, social-emotional and adaptive-behavior, the sample provided an absolute accuracy of 12-13%, showing that a larger sample size could have improved the accuracy of the scores.

Thus, it was concluded that very low birth weight preterm infants presented an expressive rate of developmental delays at the corrected age of 18-24 months, and the most frequent abnormalities were found in language, and in adaptive and social-emotional behavior. The variables CDE socio-economic class, periventricular leukomalacia, bronchopulmonary dysplasia and male sex contributed to reduce the development scores assessed by Bayley III.

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