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Original article

Variables which influence the neurodevelopment at 2 years of newborns born less than 32 weeks of gestational age or less than 1,500 g

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Abstract

Introduction: Children with very low birth weight have a high risk of complications in the neonatal period and neurodevelopment impairment is a major sequel.

Objective: To analyze how perinatal variables influence neurodevelopment at 2 years of age in newborns with less than 32 weeks of gestational age (GA) or less than 1,500 g at birth.

Methods: Retrospective descriptive study of all records of the National Registry of Very Low Weight (VLBWNT) and clinical information from 2009 to 2012. We considered a major sequel: the need for auditory prosthesis, blindness, cerebral palsy or developmental quotient below 80. Statistical analysis performed with STATA® v13, considering a level of statistical significance of 0.1.

Results: Registration of 348 newborns. Exclusion of 88: 26 transferred and 62 deaths. Of the 260 included, 152 (58.5%) had a regular follow-up. There were no significant differences between groups with or without follow-up, except for SNAPPE 2 index and patent ductus arteriosus persistence. The p50 of the GA was 30 w, the p50 of the birth weight was 1,200 g and 62% did not have major sequels. The female gender has a lower risk of sequels, compared to male (OR 0.5493; p: 0.0990). The presence of grade 3 intraperiventricular hemorrhage (IPVH) represents an 11-fold higher risk of sequels, compared to grade 0 (OR 11.78; p: 0.002)

Conclusion: An assessment at 2 years of age showed a high percentage of children with sequels, being at greater risk the male gender and severe

IPVH. This study is important because it brings information important to organize the health system in order to meet the special needs of this population.

Keywords

Very low birth weight, neurodevelopment, prematurity, sequel.

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Introduction

The evolution of maternal-fetal and neonatal medicine has led to an increase not only in the number of preterm infants but also in their survival [1-6].

After birth, premature infants are submitted to a high technology environment, essential for their survival, but which can put at risk the normal development of different organs, namely the brain [4]. Consequently, prematurity is associated with a high risk of sequels, including neurodevelopment impairment [1, 4, 8-10]. Cerebral palsy, blindness and deafness are the most important sequels; nevertheless, cognitive deficit alone is one of the most important sequels [1, 11]. Beside gestational age (GA) and birth weight, the factors associated with a sequel in neurodevelopment are major cerebral lesions (grade 3 intraperiventricular hemorrhage [IPVH], cystic periventricular leukomalacia), pulmonary bronchodysplasia, retinopathy of prematurity and sepsis [3, 4, 9, 12]. It seems that prenatal corticosteroid and maternal breastfeeding are protector factors in neurodevelopment [9, 12]. The risk factors are cumulative, so it is essential to optimize neurodevelopment of these children with follow-up programs, family support and special programs of intervention [5].

We aimed to assess the perinatal variables that influence the neurodevelopment outcome at 24-30 months of age in newborns with less than 32 weeks of GA or less than 1,500 g at birth.

Methods

Retrospective descriptive study carried out by reviewing the Data of the Very Low Birth Weight National Network (VLBWNT) and the clinical information of the newborns from 2009 to 2012.

Deaths were excluded, as were children transferred to another hospital or who did not have a follow-up at 2 years on the VLBWNT.

Comparing the groups with and without follow-up at 2 years, no significant differences were found except for the SNAPPE 2 index (p: 0.049) and the persistence of the ductus arteriosus (p: 0.037) (**Tab. 1**).

The evaluated perinatal variables were considered according to the definitions of the VLBWNT glossary [13]. We defined "moderate to severe sequel" when one or more of the following criteria were met: need for hearing aids/deafness, blindness, cerebral palsy or developmental quotient below 80 (obtained through Schedule of Growing Skills II – SGS-II) [14] at 24-30 months.

SGS-II is essentially a screening scale, which evaluates psychomotor development in 10 key areas: passive posture, active posture, locomotion, manipulation, vision, hearing, speech/language, social interaction, personal autonomy and cognition. The quotient is obtained by the ratio of the average of the quotations (functional age in months) in the various areas and the chronological age in months. An average value of 100 and a standard deviation (SD) of 15 are allowed.

Statistical analysis was performed with STATA® v13, considering a level of statistical significance of 0.1.

Results

Of the 348 newborns in the VLBWNT, 88 were excluded: 62 deaths, 26 transferred to other units (**Fig. 1**).

108 (41.5%) had no follow-up at 2 years of age.

Of the 152 children that had follow-up, 49.3% were male, with GA between 24 and 31 weeks and 6 days (median: 27 weeks and 6 days) and with a median weight of 1,200 g (500-1,920 g).

During the follow-up period, 45 (29.6%) were hospitalized in a total of 59 hospital admissions. The respiratory pathology was the most frequent cause (54.2%), followed by gastrointestinal infections

Table 1. Comparison between the groups with and without follow-up.

		Follow-up (n = 152)	No follow-up (n = 108)	p-value
Male		49.3 %	54.6%	0.45
GA (p50), weeks		27.9 (24.1-31.8)	28.3 (25-31.6)	0.3
Birth weight (p50), g		1,200 (500-1,199.3)	1,282 (530-1,243.1)	0.251
CRIB (p50)		1 (0-1.8)	1 (0-1.6)	0.467
SNAPPE 2 (p50)		22 (0-80)	15 (0-101)	
High > 29		63 (42.6%)	32 (29.9%)	0.049
PDA		33.6%	21.5%	0.037
NEC		5.9%	4.7%	0.784
Late sepsis		45%	38.3%	0.308
Oxygen therapy at 36 w		19.4%	12.8%	0.313
IPVH	**0**	71.5%	72%	0.269
	1	15.5.%	15%	
	2	4.6%	9.3%	
	3	7.9%	3.7%	
ROP	**0**	74.8%	79.2%	0.888
	1	8.9%	7.3%	
	2	13.3%	11.5%	
	3	3%	2.1%	
Prenatal steroids		29.3%	33.3%	0.562

GA: gestational age; CRIB: clinical index for babies; SNAPPE 2: score for neonatal acute physiology perinatal extension II; PDA: persistent ductus arteriosus; NEC: necrotizing enterocolitis; IPVH: intraperiventricular hemorrhage; ROP: retinopathy of prematurity.

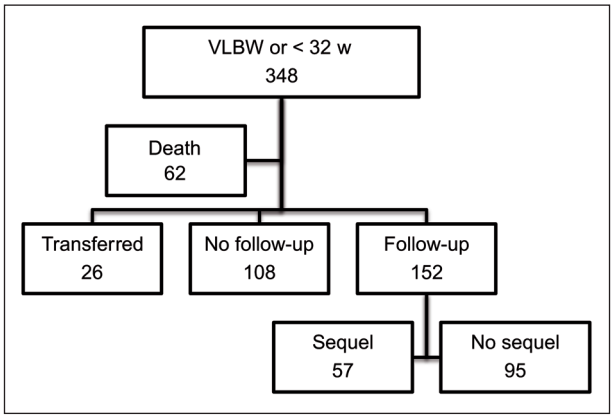


Figure 1. Population in the study.
VLBW: very low birth weight.

(16.9%) and urinary infections (5%). Two children were hospitalized with nutritional issues.

Regarding respiratory pathology, bronchiolitis (21.7%) and other pathologies associated with bronchospasm (15.8%) were the most frequent. 24.3% had a history of bronchodilator administration.

About 13.6% were hospitalized for surgical reasons, namely correction of hypospadias and inguinal hernias. One child needed gastrostomy.

After discharge no child needed parenteral nutrition, dialysis, home ventilation, or oxygen therapy.

Congenital malformations were described in 10 (6.6%) children, one of them with a description of more than one.

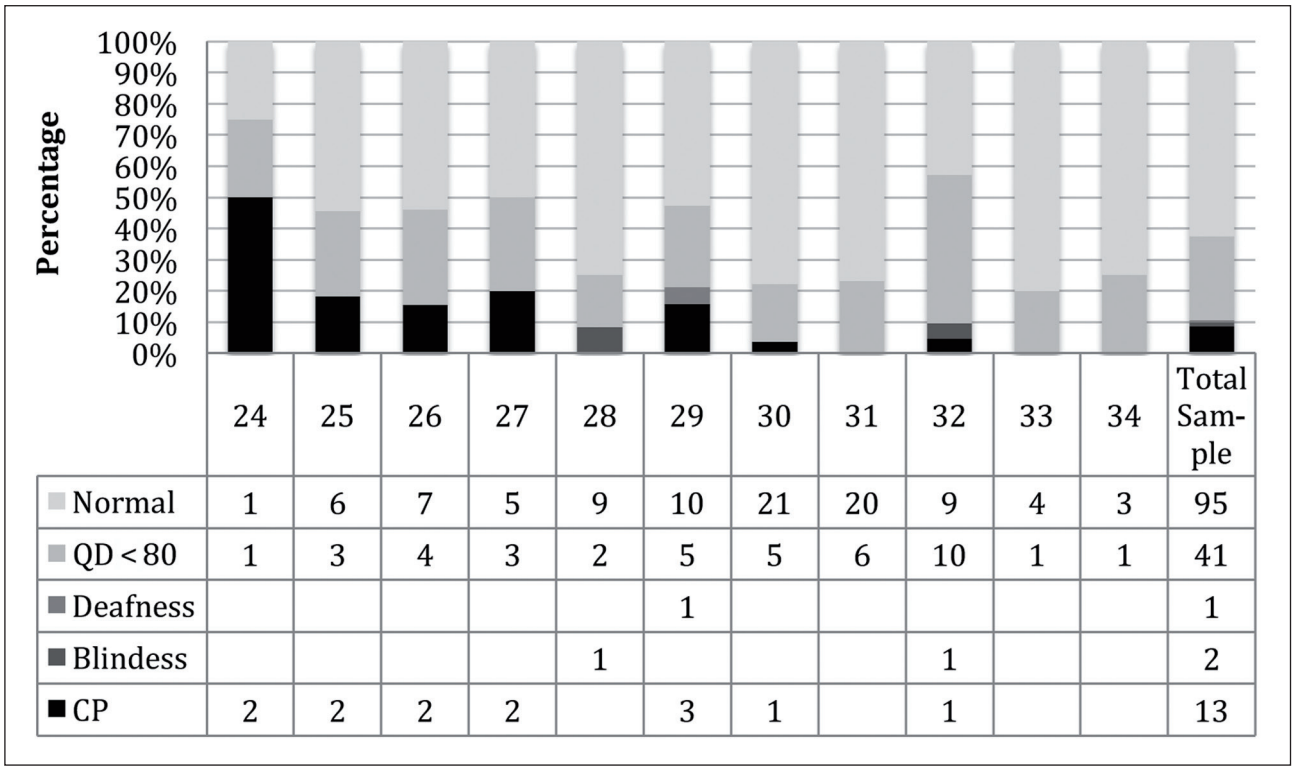
Overall, 57 (37.5%) had moderate to severe sequels, and their distribution was heterogeneous at different GAs (**Fig. 2**). The other 95 (62.5%) did not have sequels or have minor sequels.

Thirteen (22.8%) had cerebral palsy, 2 (3.5%) were diagnosed with blindness and 1 (1.8%) had deep or severe deafness requiring a hearing aid. In the formal evaluation at 2 years, 41 (71.9%) had a developmental ratio lower than 80.

Minor neurological sequels (microcephaly, hydrocephalus and cerebral atrophy) were described in 11 (7.2%) children.

After discharge, 47 (30.9%) required some developmental therapy. 26 (17.1%) integrated the early intervention program, 5 (3.3%) were admitted to a rehabilitation center, 21 (13.8%) needed physical therapy, 30 (19.7%) speech therapy and 19 (12.5%) occupational therapy, among others.

Regarding neurodevelopment (**Tab. 2**), the female gender is 45% less likely to develop sequels, compared to male gender (OR 0.5493; p: 0.099) (**Fig. 3**). On the other hand, the presence



	24	25	26	27	28	29	30	31	32	33	34	Total Sample
Normal	1	6	7	5	9	10	21	20	9	4	3	95
QD < 80	1	3	4	3	2	5	5	6	10	1	1	41
Deafness						1						1
Blindess					1				1			2
CP	2	2	2	2		3	1		1			13

Figure 2. Sequel distribution by gestational age (GA).
QD: quotient of development; CP: cerebral palsy.

Table 2. Comparative analysis of the variables influencing the presence of sequelae.

		Odds Ratio	Std. Error	p	95% Conf. Interval	
					Upper	Lower
Gender		0.5493	0.190	0.099	0.287	1.089
GA		0.987	0.009	0.174	0.969	1.006
Birth weight		1.000	0.001	0.417	0.999	1.001
CRIB		1.119	0.076	0.096	0.980	1.278
SNAPPE 2		1.015	0.009	0.098	0.997	1.034
SNAPPE 2 cathegory		1.270	0.438	0.487	0.647	2.495
PDA		0.618	0.217	0.171	0.310	1.230
NEC		0.277	0.202	0.078	0.066	1.155
Late sepsis		0.648	0.220	0.201	0.334	1.260
Oxygen therapy at 36 w		0.596	0.299	0.302	0.223	1.593
IPVH	**1**	1.2588	0.642	0.6300	0.542	3.429
	2	5.5811	4.900	0.0480	1.048	30.798
	3	11.7818	9.117	0.0020	2.358	54.753
ROP	**1**	0.9853	0.638	0.9820	0.277	3.506
	2	2.4632	1.278	0.0820	0.891	6.812
	3	5.9118	6.939	0.1300	0.592	58.994

GA: gestational age; CRIB: clinical index for babies; SNAPPE 2: score for neonatal acute physiology perinatal extension II; PDA: persistent ductus arteriosus; NEC: necrotizing enterocolitis; IPVH: intraperiventricular hemorrhage; ROP: retinopathy of prematurity.

of grade 3 and 2 IPVH represents an 11- and 5-fold, respectively, higher risk of sequels than grade 0 (OR 11.78, p: 0.002; OR 5.58, p: 0.048, respectively).

There was no correlation between the development of sequels and the remaining variables, both GA and birth weight, severity indexes (CRIB and SNAPPE 2), persistent ductus arteriosus, need for

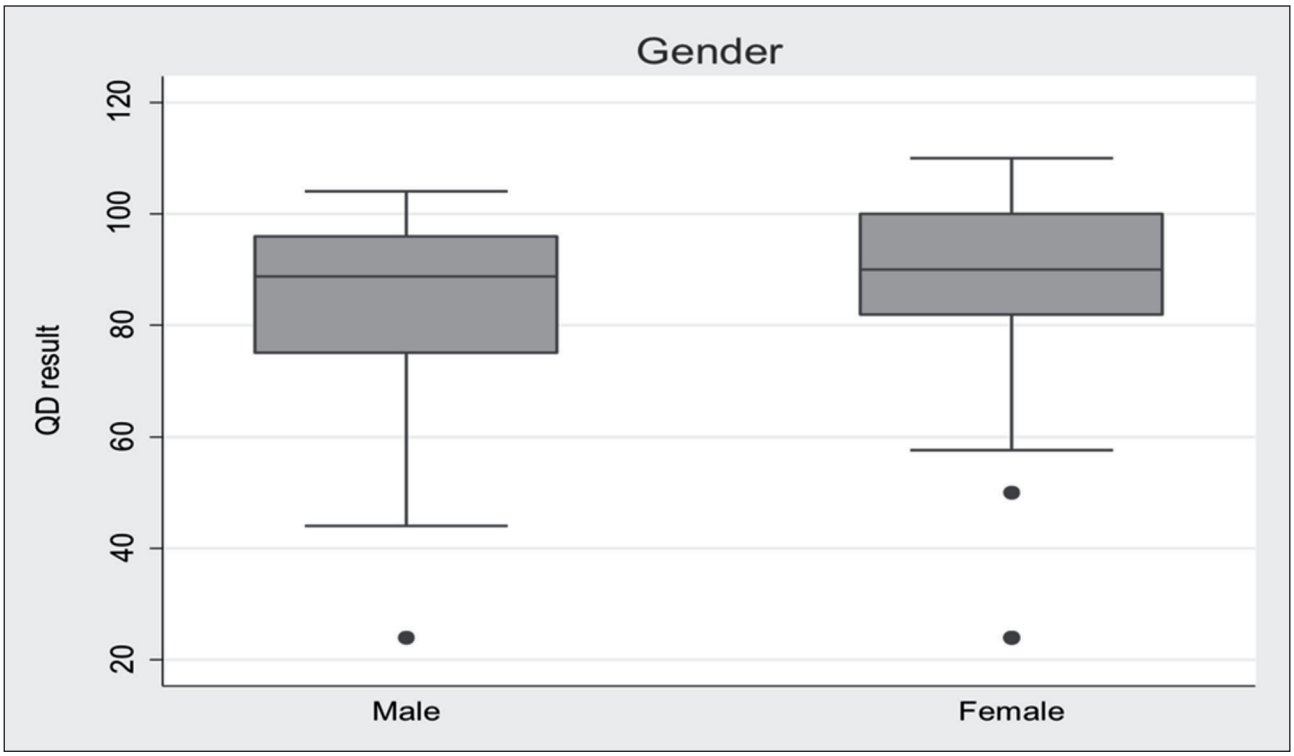


Figure 3. Box-plots distribution of the quotient of development (QD) by sex.

oxygen up to 36 weeks, late sepsis, necrotizing enterocolitis, retinopathy and prenatal corticosteroids.

We also found a significant correlation between the degree of maternal education and the developmental quotient, absence of cerebral palsy and blindness. Therefore, the higher the academic level of the mother was, the better was the development quotient of the child and the probability of cerebral palsy and blindness was lower (significant Spearman correlation with negative coefficient: -0.186). There was no correlation between sequels and father's education or profession.

Discussion

In this study, the rate of follow-up is lower (58.5%) than in other studies [2, 9]. This is a big limitation of our study, because of possible biases of lost cohort [11]. We try to minimize it comparing the two groups, which seemed similar.

In our study, the sequel rate was 37.5%, also higher than in other studies [2, 6, 8, 9]. This comparison must be made cautiously, because the used methodology, scales and population are different in the different studies [10].

In most literature the rate of severe sequels are higher in extremely preterm babies when compared to late preterm; however, in our study this difference was not statistically significant [4, 9, 11, 16-19]. Moreover, GA did not emerge as an important predictor in individual studies with preterm subgroups defined by GA and was not significant in other studies [1, 20]. One explanation is the inclusion of only the preterms of 32 weeks or less, because the prevalence of sequels declines quite steeply after 32 weeks [20, 21].

As in other studies, male gender and severe IPVH (2 and 3) were correlated with poor neurodevelopment [1, 2, 8, 9, 15, 16, 29, 22-26]. However, in our study there was no relation with birth weight, bronchopulmonary dysplasia, retinopathy or late sepsis as in other studies [2, 8, 9, 15, 19, 22, 23-25].

The recognition of the deleterious effect of the high technology environment of neonatal intensive care units has led to the adoption of neuroprotective strategies, such as the NIDCAP (newborn individualized developmental care and assessment program) [2, 9, 27]. In our unit we use our own guidelines to prevent brain hemorrhages in the first 7 days of life, in which we established the need for a quiet environment, proper positioning and minimal manipulation, among other measures. After that critical period other measures like skin-to-skin contact, minimal painful interventions and promotion of breast milk are maintained in order to promote healthy neurodevelopment. These attitudes

are not registered, so they were not evaluated in our study.

After discharge, neurodevelopment is influenced by social and environmental factors. Several studies show an association between low familiar education levels and worst cognitive development of the preterm baby, which is probably due to genetic and educational factors [1, 9, 23]. In our study mother's higher education is correlated with a better developmental quotient at 2 years, as well as with lower rates of cerebral palsy and blindness. Resende et al. [9], in another Portuguese study, showed a 5.9-fold higher risk of moderate to severe impairment of neurodevelopment in premature from mothers with low levels of education. In the same way, other studies found that maternal education background is a strong predictor of neurodevelopment and intelligence in preterm children [12, 23, 25, 28].

There seemed to be no correlation between sequels and father's education or profession in our study. This might be due to the main role of the mother in children's education in our population or because education and profession are poor markers of the whole social and genetic environment affecting the child.

To promote better long-term neurodevelopment, our unit developed a multidisciplinary program of early intervention, which includes neonatologists, physiatrists, physiotherapists and nurses. The intervention begins during hospitalization and an individualized intervention is continued after discharge aiming for the optimization of neurodevelopment of the premature child. However, similar to the protocol to prevent brain hemorrhage, no registrations were made and its influence could not be studied.

In addition to a higher risk of neurodevelopment impairment, premature babies have a higher risk of other comorbidities [1, 11]. In our study this was shown by a high rate of hospitalization (29.6%) in the first 2 years. Our rate of hospitalization is slightly lower than in another Portuguese study (26.9% vs. 38.3) [5], but the respiratory problems are the main reason in both [8, 22].

The special needs of these children born preterm are higher (30.9%) when compared with term newborns. Usually, they need multiple areas of intervention: physiotherapy, speech therapy, educational and occupational therapy. Therefore the organization of an early intervention system would allow a faster and better response, improving the outcome in this population [29, 30].

The short time of follow-up is a limitation of our study, since some deficits emerge later in scholar age.

Conclusion

In conclusion, prematurity is a growing health care problem, with a wide range of neurological and developmental disabilities in the preterm survivors. The recognition of predictor factors is important in order to develop preventive strategies. This knowledge is also important to organize the health system so it can meet the special needs of this population.

In this study, an assessment at 2 years of age showed a higher rate of sequels in premature children, with a greater risk to the male gender, babies with severe IPVH and children from mothers with lower education levels.

To achieve a better evaluation of the variables influencing the neurodevelopment and the long-term needs of premature babies, a prospective study with more premature babies and a longer follow-up time would be beneficial.

Declaration of interest

Eugénia Matos on behalf of all the Authors declares that they have no current or potential conflict of interests that might have influenced them in the results of the present study.

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