ORIGINAL ARTICLE

Impact of Prematurity Major Morbidities in the Neurodevelopment of Preterm Infants

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Abstract

Introduction: Great prematurity and very low birth weight are risk factors to neurodevelopmental disorders. We aim to study the relation between prematurity related major complications (serious brain injury, sepsis, bronchopulmonary dysplasia, and severe retinopathy of prematurity) and neurodevelopmental disorders.

Methods: Unicentric retrospective study, with children born between 2006 and 2014, with less than 32 gestational weeks or a birth weight lower than 1,500 g and evaluated with the Schedule of Growing Skills II or Griffiths Developmental Scale, regarding their neurodevelopment. We compared isolated or combined prematurity related major complications and other biological and sociodemographic variables with neurodevelopmental disorders.

Results: From the 429 studied children, 5.6% had cerebral palsy, 1.2% deafness, and 0.2% blindness. From 330 children with complete neurodevelopment evaluation, 34 presented sequelae (10.3%). Between the 18th and 36th months of corrected age, 5% of the children with evaluation had global psychomotor development delay. In the absence, presence of one, and two or more prematurity major morbidities, the incidence of neurodevelopmental disorders was 6.0%, 14.0%, and 35.7%, respectively. Prematurity related major complications were globally associated with neurodevelopmental disorders (p < 0.001), cerebral palsy (p = 0.002), and deafness (p = 0.043). Children with two or more major conditions presented a 11.7-fold greater risk when compared to their absence. Relevant risk factors were a non-nuclear family (adjusted odds ratio = 7.3), head circumference below the 3rd percentile at 18th-36th months of corrected age (adjusted odds ratio = 6.8), prematurity related major complications (adjusted odds ratio = 4.8), low maternal education (adjusted odds ratio = 4.0), and monochorionic twins (adjusted odds ratio = 3.4).

Discussion: Prematurity related major complications increases the risk of neurodevelopmental disorders. The association of major conditions significantly increases that risk. Non-nuclear family and low maternal education were associated with a higher risk of neurodevelopmental disorders.

Keywords: Child Development; Infant, Premature, Diseases/complications; Infant, Premature; Infant, Very Low Birth Weight; Neurodevelopmental Disorders/etiology; Portugal; Risk Factors

Introduction

Great prematurity and very low birth weight are risk factors for neurodevelopmental disorders.[1-7] Prematurity is also associated with learning impairments, neuromotor dysfunction, and hyperactive and attention deficit disorders in the school age.[7]

Neurodevelopmental disorders incidence varies among studies due to the different methodologies used, from 12.4% to 57.5% when assessed in the 2nd year of corrected age in the extreme prematurity birth population.[8]

Besides gestational age and birth weight, there are other biological factors associated with neurodevelopmental disorders, namely major brain injuries,[5,9-11] which includes grade 3 or superior peri-intraventricular hemorrhage,[5,9,12-14] cystic periventricular leukomalacia,[3,5,9,13-19] and periventricular venous hemorrhagic stroke,[17] but also bronchopulmonary dysplasia (BPD),[9,18] severe retinopathy of prematurity (ROP)[3,9,11,13] and sepsis.[9,13,19,20] The association of several comorbidities, also called prematurity related major complications, is strongly associated with short and long-term greater risk of neurodevelopmental disorders.[11,21,22] However, prematurity is still related to

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neurodevelopmental disorders even in the absence of prematurity related major complications (low biological risk).[2,7] In fact, when compared to term born infants, a reduction in cortical regional gray and white matter was found.[23] Those cortical differences were correlated with the existence of global intellectual performance impairments.[24]

Immature brain development, after the neonatal stage, is dependent on biological and environmental factors. Low maternal education[10,14] and inter-hospital transportation to a differentiated care maternity[20] are independent risk factors to severe neurodevelopmental impairments.

Low socioeconomical level was considered to have a negative impact on cognitive development, even after controlled for brain injuries and other medical conditions.[10]

Our aim was to identify neurodevelopmental disorders in premature infants, in the short term, considering the existence or absence of prematurity related major complications (PRMP). We also studied the associated risk of social and environmental variables for the existence of neurodevelopmental disorders.

Methods

Observational analytic retrospective study of very preterm infants (gestational age < 32 weeks) or very low birth weight (birth weight < 1,500 g) infants, born in a differentiated perinatal care hospital, between 1 January 2006 and 31 December 2014, based on the analysis of follow-up clinical visit data of those infants.

We considered prematurity related major complications as the presence of any of the following: brain injury, bronchopulmonary dysplasia, retinopathy of prematurity, and sepsis. Major brain injury included cystic periventricular leukomalacia[25] or severe peri-intraventricular hemorrhage (three or superior), or hemorrhagic venous.[26] Bronchopulmonary dysplasia was defined as the maintained need of supplementary oxygen at post-menstrual 36 weeks of age[27]; and sepsis as clinical and laboratorial presence of infection, requiring antibiotics for more than five days, with or without confirmatory hemoculture.[20] Retinopathy of prematurity of three or superior was classified as severe (international criteria).[28]

Children with electronic clinical registry of epilepsy, major, or genetic malformations were excluded from the study.

Other biological and sociodemographic characteristics studied were maternal age; single parenthood; maternal education; assisted conception; pregnancy vigilance; pregnancy related maternal diseases (pre-eclampsia, eclampsia, gestational hypertension); prenatal antibiotics; pre and postnatal corticosteroids; infectious risk; placental abruption; chorioamnionitis; premature membrane rupture; twinning and if monochorionic; place and type of birth; gestational age; gender; if light for gestational age; weight, length and head circumference development; prematurity related major complications; Apgar index in the first, fifth and tenth minute of life; first 24 hours of life death prognosis, assessed by the clinical risk index for babies (CRIB)[29]; tracheal intubation; ventilation, their types and duration; necrotizing enterocolitis; days in the maternity; maternal milk ingestion in the first three days and in maternity discharge. We considered light for gestational age when the relation between birth weight and gestational age was below 3rd percentile (P3) in the Fenton growth charts.[30] We considered extreme maternal age as pregnancy under 21 and above 35 years old; basic education if the women had completed the 9th grade or below; and a non-nuclear family if the child resided with only one of the parents, was under the grandparents' responsibility or institutionalized. Weight, height/length, and head circumference were evaluated between the 18th and 36th months of corrected age.[31]

Neurodevelopmental disorders included cerebral palsy diagnosis, neurosensorial hearing loss requiring prosthetics, blindness, and global psychomotor developmental delay. Cerebral palsy was established according to international classifications[32] and by the gross motor function classification system[33] and always confirmed by an experienced neuropediatric physician. Blindness was defined as a visual accuracy below 1/20 in the best eye.[34] Psychomotor global developmental delay was defined as a global developmental quotient (GDQ) below 70.

We obtained the GDQ from the infant's evaluation with Schedule of Growing Skills II (SGS II) or Griffiths Mental Development Scales – Extended Revision (GR).[35] The first is a commonly used psychomotor development evaluation scale that includes motor, cognitive, and social skills. It covers ten key areas, namely passive posture, active posture, locomotion, manipulation, vision, hearing, speaking, social interaction, independence, and cognitive function. The GDQ consists in the mean value (functional age in months) of the multiple areas, divided by the corrected age, in months. Higher results correspond to better functioning levels. The scale considers a mean value of 100 and a standard deviation of 15, where GDQ values of 70 are considered pathological.[35]

The GR scale is composed of six subscales, namely locomotion, socialization, language, hand-eye

coordination, fulfillment, and practical reasoning. The results for each subscale can be converted in percentiles, *z*-scores, equivalent age, and GDQ.[35]

The evaluation with SGS II and GR was performed by professionals with large proficiency and recognized validation in their application.

We used IBM SPSS 22.0® software for statistical analysis. A Mann-Whitney U test was used to compare the medians of quantitative variables between two independent samples. A chi-square test (or Fisher's test) was used to compare the qualitative variables and the existence of neurodevelopmental disorders with prematurity related major complications individually or combined. We created a logistic regression model and analyzed the odds ratio, for the variables that presented significant statistical association, to ponder its relation, with the studied outcomes. A p value < 0.05 (two-tailed) was considered as statistically significant.

Results

We studied 429 infants with at least one psychomotor evaluation from birth to the 5th year of corrected age, whose characteristics are described in Table 1.

Infants were predominantly born by caesarean (65.7%), with a mean gestational age of 29.5 weeks (23-36 weeks) and a mean birth weight of 1,235.3 g (440-2,185 g). Prenatal corticosteroids were administered to 88.8% of the mothers. Differentiated perinatal support was needed in the majority of the cases, including non-invasive (61.1%) or invasive (40.3%) ventilation.

Prematurity related major complications distribution is shown in Table 2. The most frequent was neonatal sepsis, with 82 infants affected (19.1%), followed by brain injury with 46 infants in 376 (12.2%).

From the clinical variables studied between the 18th and 36th month of corrected age, only the existence of cerebral palsy (p = 0.002) and deafness (p = 0.043) were associated with to prematurity related major complications as shown in Table 3.

Thirty four of 330 infants (10.3%) presented neurodevelopmental disorders. Twenty-four of 411 (5.6%) had cerebral palsy. In 424 infants, five had hearing loss requiring prosthetics (1.2%) and one (0.2%) was blind. From the 18th to 36th month of corrected age, 17/340 infants (5%) presented a GDQ < 70.

In Table 4, we compare the presence of neurodevelopmental disorders combined with the existence of single or clustered prematurity related major complications. The results showed that, when clustered, they have an increased risk of 4.1 times - p < 0.001, adjusted odds ratio (aOR) 4.8 - of neurodevelopmental disorders, with brain injuries and sepsis individually, conferring an increased risk of 8.6 times (p < 0.001) and 3.1 times (p = 0.003), respectively. The identified risk for neurodevelopmental disorders conferred by the existence of one, two, or more than two major morbidities combined, is shown on Table 5. The combination of two or more morbidities, instead of the analysis of two, or three prematurity related major complications separately, is justified by the low number of infants with three or more pathologies in our sample, and in order to acquire better statistical power. From the surviving infants without brain injury, neonatal sepsis, bronchopulmonary dysplasia, and severe retinopathy of prematurity, 11/183 (6.0%) had neurodevelopmental disorders. In the presence of a single prematurity related major complications, 8/57 infants (14%, aOR 3.5) had neurodevelopmental disorders, and 10/28 (35.7%, aOR 11.9) when there were two or more morbidities.

To assess its relevance to negative neurodevelopmental outcomes, we compared the clinical and sociodemographic variables with the presence of neurodevelopmental disorders, before and after logistic regression adjustment. Monochorionic pregnancy, non-accompanied pregnancy, endotracheal intubation, supplemental oxygen need during maternity stay, invasive ventilation, ventilation duration in days, non-nuclear family, ninth grade or below of maternal education, lower Apgar indexes at the first, fifth and tenth minute, lower head circumference at birth, and a weight, length, and head circumference lower than P3 between the 18th and 36th months of corrected age, were found to be positively associated with the presence of neurodevelopmental disorders. Prenatal corticosteroids were inversely significantly associated with those disorders.

Clinical variables that resulted from the combination of others were not included in the statistical comparison, despite being present in the sample description (*i.e.* CRIB). We excluded Apgar index values at the first and fifth minutes from the regression model, for already being represented in it by the Apgar index at the 10th minute.

After logistic regression, the variables maintaining statistical significance were monochorionic pregnancy, non-nuclear family, maternal basic education, head circumference under P3 between the 18th and 36th months of corrected age, and the existence of prematurity related major complications.

Table 1. Characteristics of the studied population and a comparison between the variables and the existence of prematurity related major complications

	Global (n = 429)	With PRMP *	Without PRMP *	*p*
Maternal age (years) (mean ± SD)	30.5 ± 5.6	29.3 ± 5.8	31.1 ± 5.4	0.006
Maternal age < 18 and > 35 years (n / %)	76 / 17.7	19 / 16.2	45 / 19.1	0.559
Non-nuclear family (n / %)	23 / 5.4 (n = 423) †	10 / 8.6	10 / 4.3	0.141
Graduated mother (n / %)	124 / 32.2 (n = 385) †	36 / 34.0	65 / 29.5	0.444
Maternal basic education (n / %)	77 / 19.9 (n = 387) †	28/ 25.9	39 / 17.7	0.108
Pregnancy vigilance (n / %)	414 / 96.5	113 / 96.6	227 / 96.6	1.000
Prenatal corticosteroids (n / %)	381 / 88.8	96 / 82.1	215 / 91.5	0.013
Pre-eclampsia / maternal hypertension (n / %)	107 / 25.0 (n = 428) †	25 / 21.6	66 / 28.1	0.198
Placental abruption (n / %)	39 / 9.1	16 / 13.7	18 / 7.7	0.085
Chorioamnionitis (n / %)	29 / 6.8 (n = 426) †	10 / 8.6	12 / 5.2	0.244
Premature membrane rupture (n / %)	133 / 31.0	28 / 23.9	76 / 32.3	0.109
Twinning (n / %)	122 / 28.4	30 / 25.6	74 / 31.5	0.268
Monochorionic twinning (n / %)	51 / 11.9	14 / 12.0	33 / 14.0	0.623
Outborn delivery (n / %)	55 / 12.8	27 / 23.1	17 / 7.2	< 0.001
Vaginal delivery (n / %)	147 / 34.3	44 / 37.6	76 / 32.2	0.341
Spontaneous birth (n / %)	173 / 40.3	52 / 44.4	91 / 38.7	0.357
Gestational age (weeks) (mean ± SD)	29.5 ± 2.1	27.9 ± 1.9	30.1 ± 1.9	< 0.001
Light for gestational age (n / %)	103 / 24.0	22 / 18.8	63 / 26.8	0.112
Male (n / %)	233 / 54.3	66 / 56.4	129 / 54.9	0.821
Birth weight (g) (mean ± SD)	1235.3 ± 307.9	1028.0 ± 277.8	1301.5 ± 289.0	< 0.001
Birth length (cm) (mean ± SD)	37.3 ± 2.9 (n = 425) †	35.2 ± 2.9	38.0 ± 2.6	< 0.001
Head circumference birth (cm) (mean ± SD)	26.9 ± 2.2 (n = 425) †	25.4 ± 2.3	27.5 ± 2.0	< 0.001
Apgar first min (mean ± SD)	6.87 ± 2.1 (n = 426) †	5.9 ± 2.2	7.3 ± 2.0	< 0.001
Apgar fifth min (mean ± SD)	8.89 ± 1.2 (n = 423) †	8.3 ± 1.4	9.1 ± 1.0	< 0.001
Apgar 10th min (mean ± SD)	9.40 ± 0.8 (n = 420) †	9.0 ± 1.0	9.6 ± 0.7	< 0.001
Reanimation (n / %)	219 / 51.0	86 / 73.5	95 / 40.9	< 0.001
Neonatal reanimation with EI (n / %)	118 / 27.5	64 / 54.7	47 / 20.0	< 0.001
Erythrocyte transfusion (n / %)	87 / 20.3	55 / 47.0	22 / 9.4	< 0.001
Postnatal corticosteroids (n / %)	43 / 10.0 (n = 428) †	96 / 82.1	215 / 91.5	0.013
CRIB ≥ 5 (n / %)	62 / 14.8 (n = 420) †	43 / 37.4	14 / 6.0	< 0.001
CRIB (mean ± SD)	1.96 ± 2.5 (n = 420) †	3.9 ± 3.1	1.3 ± 1.6	< 0.001
CPAP (n / %)	258 / 60.1	102 / 87.2	115 / 48.9	< 0.001
Oxygen during hospitalization (n / %)	266 / 62.0	98 / 83.8	126 / 53.6	< 0.001
Invasive ventilation (n / %)	173 / 40.3	87 / 74.4	63 / 26.8	< 0.001
Non-invasive ventilation (n / %)	262 / 61.1	103 / 88.0	117 / 49.8	< 0.001
Surfactant (n / %)	145 / 33.8	75 / 64.1	56 / 23.8	< 0.001
CMV (days) (mean ± SD)	2.1 ± 5.8	5.8 ± 9.6	0.7 ± 2.3	< 0.001
Non-invasive ventilation (days) (mean ± SD)	7.6 ± 13.7 (n = 428) †	17.8 ± 19.1	3.7 ± 7.7	< 0.001
Maternal milk at the third day (n / %)	259 / 61.1 (n = 424) †	40 / 34.5	170 / 72.6	< 0.001
Maternal milk on discharge (n / %)	368 / 85.8	95 / 81.2	211 / 89.8	0.029
Medical PAD (n / %)	75 / 17.5 (n = 428) †	21 /17.9	13 / 5.5	< 0.001
Hospitalization duration (days) (mean ± SD)	48.6 ± 23.8 (n = 414) †	67.9 ± 25.7	42.8 ± 19.5	< 0.001
Necrotizing enterocolitis (n / %)	5 / 1.2	5 / 4.3	0 / 0	0.004

CMV - conventional mechanical ventilation; CPAP - continuous positive airway pressure; CRIB - clinical risk index for babies; EI - endotracheal intubation; PAD - persistent arterial *ductus*; PRMP - prematurity related major complications; SD - standard deviation.
* Total n dependent on the number of children with prematurity related major complications and tested independent variable registry.
† Total n different than 429, due to registry omissions.
P value using the chi-square test or Fisher's test for the qualitative variables and the Mann-Whitney U test for the quantitative variables.

Discussion

Our sample is similar to other authors, except for the rate of twins, which was greater in ours, and prematurity related major complications (bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, and sepsis), which was lower in our study.[36] This may reflect having studied a larger sample. As expected, infants with prematurity related major complications were more immature, had more morbidity, and longer maternity stays.

The prevalence of cerebral palsy in our study was 56/1,000, which is in line with the Europe reported prevalence of 50.1-79.5/1,000 in premature children born with less than 32 weeks of gestation,[37] and the Portugal prevalence of 57.2/1,000.[38]

Regarding our study objective, to compare the neurodevelopment of preterm children with or without prematurity related major complications, we observed that the accumulation of prematurity related major complications is positively related to worse prognosis, as seen in other studies.[11,21,22,39] In the literature, prematurity related major complications is associated with increased mortality and a higher incidence of neurodevelopmental disorders. As our work excluded fatalities, we obtained a reduced number of children with more than two associated pathologies, who could have had neurodevelopmental disorders diagnosis in their lifetime, thus biasing prevalence data.

We identified a larger prevalence of cerebral palsy and deafness, but not global psychomotor developmental delay between the 18th and 36th months of corrected age, when infants had prematurity related major complications. It is surprising that, in our sample, we found no statistically significant differences between the presence or absence of those pathologies and the existence of a global developmental delay. When we

Table 2. Prematurity related major complications in the study

Prematurity related major complications	n / % *
Neonatal sepsis	82 / 19.1 (n = 429)
Severe brain injury †	46 / 12.2 (n = 376) §
Peri-intraventricular hemorrhage > 3 †	21 / 5.0 (n = 424) §
Cystic periventricular leukomalacia > 1	14 / 3.3 (n = 427) §
Bronchopulmonary dysplasia (O2 36S)	18 / 4.7 (n = 379) §
Retinopathy of prematurity > 2 ‡	10 / 2.6 (n = 378) §

* Total n dependent on the number of children with prematurity related major complications registry.
† Percentage that had transcranial sonography.
‡ Percentage with ophthalmological observation.
§ Total n different than 429, due to registry omissions.

Table 3. Comparison between clinical follow-up and prematurity related major complications

	n / % (n with registry)	With PRMP *	Without PRMP *	*p*
Follow-up between the 18th and 36th months of corrected age				
Weight < P3	78 / 20.6 (n = 378) †	29 / 27.6 (n = 105) †	41 / 19.6 (n = 209) †	0.108
Length < P3	113 / 29.9 (n = 378) †	38 / 36.2 (n = 105) †	64 / 30.6 (n = 209) †	0.320
Head circumference < P3	20 / 5.3 (n = 375) †	8 / 7.8 (n = 102) †	11 / 5.3 (n = 209) †	0.372
GDQ < 70	17 / 5.0 (n = 340) †	8 / 8.6 (n = 93) †	7 / 3.7 (n = 190) †	0.095
Follow-up between 0-5 years of corrected age				
Cerebral palsy (n / %)	23 / 5.6 (n = 411) †	14 / 12.3 (n = 114) †	7 / 3.1 (n = 223) †	0.002
Deafness (n / %)	5 / 1.2 (n = 424) †	4 / 3.5 (n = 115) †	1 / 0.4 (n = 232) †	0.043
Blindness (n / %)	1 / 0.2 (n = 424) †	1 / 0.9 (n = 115) †	0 / 0 (n = 232) †	0.331

GDQ - global psychomotor developmental quotient; P - percentile; PRMP - prematurity related major complications.
* Total n dependent on the number of children with prematurity related major complications and tested independent variable registry.
† Total n different than 429, due to registry omissions.
p value using the chi-square test or Fisher's test for the qualitative variables and the Mann-Whitney U test for the quantitative variables.

Table 4. Comparison between a prematurity related major complications existence and neurodevelopmental disorders

	Neurodevelopmental disorders	X^2	OR (CI 95%)	*p*	aOR (95% CI) *
	n / total (%)				
PRMP (n = 278) †					
Present Absent	20 / 95 (21.1) 11 / 183 (6.0)	14.3	4.2 (1.9- 9.1)	< 0.001	4.8 (1.5-15.1)
Brain injury (n = 293) †					
Present Absent	14 / 37 (37.8) 17 / 256 (6.6)	33.3	8.6 (3.7-19.6)	< 0.001	
Sepsis (n = 331) †					
Present Absent	14 / 67 (20.9) 20 / 264 (7.6)	10.3	3.1 (1.5-6.4)	0.003	
BPD (n = 295) †					
Present Absent	2 / 16 (12.5) 31 / 279 (11.1)	0.03	1.1 (0.2-5.3)	0.696	
ROP (n = 295) †					
Present Absent	2 / 9 (22.2) 28 / 286 (9.8)	1.48	2.5 (0.5-12.8)	0.230	

aOR - adjusted odds ratio; BPD - bronchopulmonary dysplasia; CI - confidence interval; OR - odds ratio; PRMP - prematurity related major complications; ROP – retinopathy of prematurity; X^2 - chi-square.
* aOR - logistic regression model adjusted odds ratio, and to a total n of 240 children with data for every variable studied, and including: 10th minute Apgar index; monochorionic twinning; head circumference at birth; prenatal corticosteroids; non-supervised pregnancy; invasive ventilation; weight, length and head circumference below the 3rd percentile between the 18th and 36th months of corrected age; basic maternal education; non-nuclear family and prematurity related major complications.
† total n different than 429, due to registry omissions
Odds ratio using the chi-square test or Fisher's test for variable association.

Table 5. Isolated or in association prematurity related major complications impact on the existence of neurodevelopmental disorders

Prematurity related major complications	Neurodevelopmental disorders (n = 264) *		
	n / total n (%)	aOR†	95% CI
Absent	11 / 183 (6.0)		
Isolated major pathology ‡	8 / 57 (14.0)	3.5	(1.2-9.8)
Two or more major pathologies ‡	10 / 28 (35.7)	11.9	(4.2-33.9)

aOR - adjusted odds ratio; CI - confidence interval; OR - odds ratio.
* Total n different than 429, due to registry omissions.
† aOR - adjusted odds ratio to a total n of 264 children with registered data to the studied variables: one prematurity related major complications and two or more premature related major complications.
‡ When the existence of prematurity related major complications was unknown due to the registry omission of one of the pathologies included in this cluster, the event was excluded from the analysis. However, cases with more than one prematurity related major complications confirmed were accepted in the analysis, even with the registry omission of any of the others.

Table 6. Comparison between clinical and sociodemographic variables and the existence of neurodevelopmental disorders

Neurodevelopmental disorders *versus* other variables (n = 333) *	With ND	Without ND	*p*	OR (95% CI)	aOR (95% CI) ‡
Maternal age in years (mean ± SD)	31.0 ± 5.3	30.7 ± 5.5	0.557		
Extreme maternal age (n / %)	5 / 14.7	54 / 18.2	0.616		
Non-nuclear family (n / %) † (n = 330)	9 / 26.5	7 / 2.4	< 0.001	14.9 (5.1-43.3)	7.3 (1.6-32.8)
Graduated mother (n / %)	10 / 24.4	98 / 36.2	0.438		
Basic maternal education (n / %) † (n = 305)	17 / 50.0	41 / 15.0	< 0.001	5.7 (2.7-12.0)	4.0 (1.4-11.6)
Assisted conception (nº / %)	2 / 5.9	28 / 9.4	0.753		
Non-supervised pregnancy (nº / %)	3 / 8.8	5 / 1.7	0.038	0.2 (0.0-0.8)	
Prenatal corticosteroids (n / %)	26 / 76.5	272 / 91.0	0.016	0.3 (0.1-0.8)	
Pre-eclampsia/maternal hypertension (nº / %) † (n = 332)	12 / 35.3	71 / 24.2	0.157		
Infectious risk (nº / %)	10 / 29.4	117 / 39.1	0.269		
Placental abruption (nº / %)	3 / 8.8	29 / 9.7	1.000		
Chorioamnionitis (n / %) †(n = 331)	2 / 5.9	20 / 6.7	1.000		
Premature membrane rupture (nº / %)	8 / 23.5	94 / 32.1	0.306		
Twinning pregnancy (n / %)	11 / 32.4	89 / 29.8	0.755		
Monochorionic twinning (n / %)	9 / 26.5	33 / 11.0	0.024	2.9 (1.2-6.7)	3.4 (1.1-10.4)
Outborn delivery (nº / %)	7 / 20.6	32 / 10.7	0.096		
Vaginal delivery (nº / %)	11 / 32.4	107 / 35.8	0.692		
Spontaneous birth (nº / %)	15 / 44.1	117 / 39.1	0.573		
Gestational age (weeks) (mean ± SD)	29.2 ± 2.1	29.6 ± 2.1	0.269		
Male (nº / %)	21 / 61.8	153 / 51.2	0.241		
Birth weight (g) (mean ± SD)	1199 ± 0.4	1231 ± 0.3	0.418		
Birth length (cm) (mean ± SD)	36.4 ± 3.0	37.3 ±3.0	0.063		
Head circumference birth (cm) (mean ± SD)	26.0 ± 2.2	26.9 ± 2.2	0.016		
Apgar first minute (mean ± SD)	6.0 ± 2.5	6.9 ± 2.1	0.030		
Apgar fifth minute (mean ± SD)	8.44 ± 1.4	8.9 ± 1.2	0.029		
Apgar 10th minute (mean ± SD)	9.0 ± 1.1	9.4 ± 0.8	0.015		
Neonatal reanimation with EI (n / %)	16 / 47.1	72 / 24.1	0.004	2.8 (1.4-5.8)	
Oxygen during hospitalization (n / %)	28 / 82.4	179 / 59.9	0.010	3.1 (1.3-7.8)	
Erythrocyte transfusion (n / %)	11 / 32.4	62 / 20.7	0.121		
Postnatal corticosteroids (n / %) † (n = 332)	6 / 17.6	28 / 9.4	0.138		
Invasive ventilation (n / %)	20 / 58.8	109 / 36.5	0.011	2.5 (1.2-5.1)	
Non-invasive ventilation (n / %)	27 / 79.4	178 / 59.5	0.065		
Surfactant (nº / %)	15 / 44.1	97 / 32.4	0.172		
CMV (days) (mean ± SD)	3.7 ± 8.2	2.1 ± 5.6	0.025		
Non-invasive ventilation (days) (mean ± SD)	10.4 ± 14.5	7.5 ± 13.7	0.029		
Necrotizing enterocolitis (n / %) (n = 329) †	0 / 0.0	5 / 1.7	1.000		
Maternal milk 3th day of life (n / %) (n = 329) †	18 / 52.9	185 / 62.7	0.267		
Maternal milk discharge (n / %)	27 / 79.4	259 / 86.6	0.295		
Medical PDA (nº / %) (n = 329) †	6 / 17.6	57 / 19.1	0.835		
Surgical intervention (nº / %)	4 / 11.8	16 / 5.4	0.134		
Hospitalization (days) (mean ± SD)	56.5 ± 26.8	48.6 ± 23.6	0.068		
Weight < P3 between 18th-36th months (n / %) (n = 309) †	12 / 38.7	58 / 20.9	0.023	2.4 (1.1-5.3)	
Length < P3 between 18th-36th months (n / %) (n = 309) †	15 / 48.4	80 / 28.6	0.023	2.3 (1.1-5.0)	
Head circumference < P3 between the 18th and 36th months (n / %) (n = 308) †	7 / 22.6	9 / 3.2	< 0.001	8.8 (3.0-25.6)	6.8 (1.5-32.0)

aOR - adjusted odds ratio; CI - confidence interval; CMV - conventional mechanical ventilation; EI - endotracheal intubation; ND - neurodevelopmental disorders; OR - odds ratio; P - percentile; PAD - persistent arterial *ductus*; SD - standard deviation.
* Total n dependent on the number of children with simultaneous neurodevelopmental disorders and independent variables tested registry.
† Total n different than 429, due to registry omissions.
‡ aOR - logistic regression model adjusted odds ratio, and to a n of 240 children with data to all the studied variables, and including: 10th minute Apgar index; monochorionic twinning; head circumference at birth; prenatal corticosteroids; non-supervised pregnancy; invasive ventilation; weight, length and head circumference below P3 between the 18th and 36th months.
p value using the chi-square test or Fisher's test for the qualitative variables and the Mann-Whitney U test for the quantitative variables.

combined neurodevelopmental categories (cerebral palsy, neurosensorial deafness, blindness, and global psychomotor developmental delay) in one variable, we still observed significant association with the existence of prematurity related major complications - chi-square (1, n = 278) = 14.281, $p < 0.001$ -, similar to other studies.[5,10,11] The clinical and sociodemographic variables we found were associated with neurodevelopmental disorders, have been correlated with them previously.[5,6,13]

When subjected to a logistic regression model, only the following variables: non-nuclear family (aOR = 7.3), head circumference below P3 between the 18th and 36th month of corrected age (aOR = 6.8), prematurity related major complications (aOR = 4.8), basic maternal education (aOR = 4.0), and monochorionic twinning (aOR = 3.4), significantly increased the risk of neurodevelopmental disorders. Other authors also found a positive association between monochorionic twinning and neurodevelopmental disorders.[40] The finding that maternal education influences neurodevelopment has already been described in the literature.[3,41] Higher education can protect against the negative influences that a preterm birth might have in the mother, namely depression, psychological distress, and loss of feeling of being in control. It is speculated that low literacy, by not preventing these maternal issues, may be an adverse factor to premature infants' neurodevelopment.[42] These mothers may be less prone to provide meaningful psychomotor stimulation and have lower financial resources to seek, the eventually needed, supportive therapies. These factors as well as access, type, and quality of the existing therapies should be addressed in futures studies in order to understand their real impact on the prevalence and reduction of neurodevelopmental disorders in this population.

Head circumference, by reflecting brain growth, is particularly relevant and considered as one of the most consistent markers in neurodevelopment prognosis.[43,44]

Our study strengths include having a medium size sample, in which we thoroughly detailed the neonatal, clinical, and sociodemographic factors, which allowed for an extended multifactorial analysis. However, it has limitations that reduce the confidence of our conclusions. Particularly, being a retrospective unicentric study, which may not reflect the current practice in prematurity neonatal care and being subjected to the already gathered and registered data, which restrained the uniformization of the evaluation timing and impeded the correction of any registry failure, altering the sample size for some variables and in some of the statistical tests used. By not comparing the results to a term born infants sample, we could not infer differences in the neurodevelopment between those populations. The high variability in the evaluation timing between infants limited the possibilities of grouping and distributing them according to gestational age. Moreover, the sample was heterogeneous in many of its characteristics, including prematurity related major complications, which hinders results generalization. Another limitation was the use of two distinct evaluation tests (SGS II and GR) with most of the children fulfilling SGS II as a screening test, and only in selected cases performing the GR. In addition, by including only the neurodevelopment evaluation tests results from the period between the 18th and 36th months of corrected age in the study, we lost test sensitivity, which is superior in more advanced ages. This may conceal the existence of children with apparent normal neurodevelopment, which in subsequent evaluations manifested disorders.

Very preterm infants or those with very low birth weight who suffer from prematurity related major complications (mainly with a combination of two or more pathologies), present a higher risk of neurodevelopmental disorders, especially with accompanying non-nuclear family, low maternal education, monochorionic twinning, or head circumference below the 3rd percentile between the 18th and 36th months of corrected age.

WHAT THIS STUDY ADDS

- Prematurity related major complications is associated with the existence of neurodevelopmental disorders in very preterm infants or with very low birth weight, mainly when those pathologies are combined.
- Non-nuclear family and low maternal education as well as monochorionic twinning and a head circumference below the 3rd percentile between the 18th and 36th months of corrected age are associated with neurodevelopmental disorders, in very preterm infants or with very low birth weight.
- The presence of two or more prematurity related major complications, associated with a non-nuclear family/low maternal education, should prompt the activation of available resources, to achieve maximal neurodevelopmental potential of the child.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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Impacto da Patologia *Major* da Prematuridade no Neurodesenvolvimento de Pré-Termos

Resumo:

Introdução: A grande prematuridade e o muito baixo peso ao nascer são fatores de risco para morbilidade e alterações do neurodesenvolvimento. Pretendemos estudar a relação entre as patologias *major* da prematuridade (lesão cerebral grave, sepsis, displasia broncopulmonar e retinopatia da prematuridade grave) e a existência de alterações do neurodesenvolvimento.

Métodos: Estudo unicêntrico retrospetivo, com crianças de idade gestacional inferior a 32 semanas ou peso ao nascimento inferior a 1500 g, nascidas entre 2006 e 2014. Avaliou-se o desenvolvimento psicomotor com a *Schedule of Growing Skills II* ou com a Griffiths *Developmental Scale*. Analisámos a associação entre a patologia *major* da prematuridade isolada ou combinada bem como outros fatores de risco biológicos e sociodemográficos com as alterações do neurodesenvolvimento.

Resultados: Das 429 crianças estudadas, 5,6% tinham paralisia cerebral, 1,2% surdez e 0,2% cegueira. Possuíam avaliação completa do neurodesenvolvimento 330 crianças, das quais 34 tinham sequelas (10,3%). Entre os 18-36 meses de idade corrigida, 5% das crianças com avaliação apresentavam atraso do desenvolvimento psicomotor. Na ausência, presença de uma e duas ou mais patologias *major* a percentagem de sequelas foi de 6,0%, 14,0% e 35,7%, respetivamente. A patologia *major* da prematuridade associou-se globalmente a sequelas no neurodesenvolvimento ($p < 0,001$), à paralisia cerebral ($p = 0,002$) e à surdez ($p = 0,043$). Crianças com duas ou mais patologias *major* da prematuridade apresentam risco de alterações do neurodesenvolvimento 11,7 vezes superior quando comparadas com a ausência dessas patologias. Identificámos como fatores de risco independentes para alterações do neurodesenvolvimento a inexistência de família nuclear (*odds ratio* ajustada = 7,3), o perímetro cefálico dos 18-36 meses inferior ao percentil três (*odds ratio* ajustada = 6,8), a patologia *major* da prematuridade (*odds ratio* ajustada = 4,8), a escolaridade materna básica (*odds ratio* ajustada = 4,0) e gemelaridade monocoriónica (*odds ratio* ajustada = 3,4).

Discussão: A patologia *major* da prematuridade aumenta o risco de alterações do neurodesenvolvimento. A associação de patologias aumenta significativamente esse risco. A inexistência de família nuclear e o baixo nível de educação materna associaram-se a risco superior de alterações do neurodesenvolvimento.

Palavras-Chave: Desenvolvimento da Criança; Doenças do Prematuro/complicações; Fatores de Risco; Portugal; Recém-Nascido de Muito Baixo Peso Recém-Nascido Prematuro; Transtornos do Neurodesenvolvimento/etiologia