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Original article

Catch-up growth in preterm neonates with bronchopulmonary dysplasia in the first 2 years of life

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Abstract

Bronchopulmonary dysplasia (BPD) is a serious problem in Neonatal Intensive Care Units (NICUs). It is a multifactorial disease that may influence the growth and development of preterm neonates. The aim of this retrospective case-control study of preterm infants with BPD who were born in our centre was to evaluate the growth of these infants in the first 2 years of life compared with healthy preterm infants and to determine risk factors associated with poor growth.

Those with major congenital malformations, congenital TORCH infection, deceased before 36 weeks of postmenstrual age or during the first 28 days of life and those who were transferred during hospitalization and outborn neonates were excluded.

A total of 90 preterm neonates were enrolled and 30 (33.3%) of them had BPD. At 12 months of corrected age, gestational age and pre-pregnancy mother's weight were shown to be associated with short stature. Weight at birth was also associated with low weight and head circumference growth. At 12 months after term, no differences were found within the growth assessment.

Our study showed that growth between 12 and 18 months of life in preterm infants with BPD was sufficient to catch up.

Keywords

Bronchopulmonary dysplasia, newborn, Neonatal Intensive Care Units, prematurity.

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Introduction

Bronchopulmonary dysplasia (BPD) is one of the most important sequelae of prematurity and the incidence rates vary according to the definition applied, population characteristics and the medical center. Data from 2015 from the Vermont Oxford Network shows that the incidence of BPD was 44% among preterm infants. In Portugal, one study with 256 newborns, with a gestational age (GA) less than 30 weeks and birth weight less than 1,250 g, admitted to 5 Portuguese units between January 1, 2004, and December 31, 2006, showed that the overall prevalence of BPD was 12.9% [1].

BPD is a multifactorial chronic lung disease that involves antenatal and postnatal risk factors, and a strong genetic component may contribute to lung alveolar and vascular development [2]. BPD has a great degree of severity and the more severe forms are associated with higher morbidity and mortality. It develops in preterm neonates treated with oxygen and positive high-pressure mechanical ventilation [3, 4]. High concentrations of inspired oxygen produce reactive oxygen species (ROS) that may lead to an inflammatory response with atelectasis, emphysema, fibrosis, reduced numbers of alveoli and pulmonary hypertension [5, 6]. The risk increases with decreasing GA and it is greater in preterm infants due to their immature antioxidant enzyme systems [7, 8]. This imbalance between lung injury and repair predisposes an increased rate of respiratory sequelae and may lead to cardiovascular and cognitive impairment, high rates of prolonged hospitalization, nutritional and neurodevelopment abnormalities and impairment in growth velocity during Neonatal Intensive Care Unit (NICU) stay and childhood [4, 5].

Catch-up growth was defined as a more accelerated growth than the median for age and sex in the first years of life that occurs in preterm neonates. In these cases, there is a significant ascending percentile crossover [9]. Although it has many limitations of reliability, anthropometry, a simple, economical and noninvasive method, is the most used to evaluate the growth after discharge from the NICU. The anthropometric measures most used in the evaluation of preterm infants are weight, length and head circumference (HC) [10].

In preterm neonates with BPD, growth failure may be related to the increase in energy deficits associated with the increased workload of breathing and difficulty in maintaining a total nutrient intake. Huysman et al. showed that growth during the first year in infants with BPD was not sufficient to catch up [11]. However, Yu et al. demonstrated that catch-up growth might be predictable with appropriate treatment [12]. Although it is desired to achieve adequate growth, rapid growth after 2 years of life could be related to a higher incidence of cardiovascular diseases, insulin resistance and obesity in adulthood. In improper intrauterine nutrition, adaptive mechanisms were developed and became maladjusted after birth, conditioning the appearance of metabolic alterations [9, 13]. Therefore, it is essential to make an early close evaluation and provide nutritional care implementation in preterm neonates after hospital discharge to avoid growth restriction and other adverse secondary sequelae [14].

There still is a lack of information regarding the effect of BPD on long-term growth in preterm infants and some trials are controversial [15-30]. Therefore, this study aims to evaluate the growth of preterm infants (< 30 weeks of GA) with BPD in the first 2 years of life compared with healthy preterm infants and to determine the risk factors associated with poor growth.

Subjects and methods

Preterm infants with BPD admitted between January 1, 2006, and October 30, 2016, to a Level III NICU were considered for this retrospective case-control study. This study was approved by the Ethics Committee of our Institution, whose chairperson is Filipe Almeida, MD, Ph.D., on September 14, 2018, with protocol number 215/18.

Inborn preterm infants with GA less than 30 weeks were considered eligible for the study. GA was assessed by menstrual age (women with regular menstrual cycles), ultrasound examination (when existing a discrepancy of 2 or more weeks between the age derived by menstrual dating and

the age derived sonographically or in the absence of a menstrual date) or by the New Ballard Score (in the absence of obstetrical indexes) [15, 16].

For the cases, we selected preterm neonates with BPD and, for the controls, we selected healthy preterm neonates. The diagnosis of BPD was considered if there was a requirement for supplementary oxygen for at least 28 postnatal days or 36 weeks of postmenstrual age [17].

Neonates with major congenital malformations, congenital TORCH (Toxoplasmosis, Others, Rubella, Cytomegalovirus, Herpes), deceased before 36 weeks of postmenstrual age or during the first 28 days of life, those who were transferred during hospitalization and outborn neonates were excluded. A total of 30 patients with BPD fit the criteria above. Two controls were selected for each case, with the same exclusion criteria, same gender, GA (more or less 2 weeks) and weight at birth (more or less 200 g). Some controls were discharged at 35 weeks to other hospitals without a diagnosis of BPD.

Data were collected retrospectively from the neonatal and obstetric database of our NICU and patients' medical files to obtain maternal, gestational and delivery data, and neonatal clinical and interventional data during hospitalization. These data are explained in **Tab. 1** [31-47].

After discharge, data were collected at the ages of 3, 6, 12, 18 and 24 months. The child growth

Table 1. Data of subjects and methods.

Major congenital malformation	Anomaly or malformation that creates significant medical problems for the patient or requires specific surgical or medical management [31].
Prolonged rupture of membranes	Rupture > 18 h before labor [32].
Abruptio placentae	Premature complete or partial separation of the placenta before delivery [33].
Clinical chorioamnionitis	Presence of maternal fever (> 38°C) associated with at least two of the following criteria: maternal leukocytosis (> 15,000 cells/mm^3), maternal tachycardia (> 100 beats per minute), fetal tachycardia (> 160 beats per minute), uterine tenderness, or a foul odor to the amniotic fluid [34].
Histological chorioamnionitis	Infiltration of polymorphonuclear and mononuclear cells in the chorion and amnion, and stage were made by the progression of disease based on anatomical regions infiltrated [35].
Use of antenatal corticosteroids	Four doses of 6 mg of dexamethasone administrated at 12 h intervals or two doses of 12 mg of bexamethasone 24 h apart. An uncomplete cycle was considered when the second dose of corticosteroid was taken more than 12 hours after the first one and a full cycle was not completed [36].
SGA	Weight at birth below the third percentile of the expected value for the corrected GA, according to Fenton's fetal growth charts [37].
Early fetal growth restriction	Isolated criteria – fetal abdominal circumference/estimated fetal weight below the third percentile for GA or umbilical artery with absent end-diastolic flow on Doppler; combined criteria – fetal abdominal circumference/estimated fetal weight below the tenth percentile for GA and the uterine and umbilical arteries pulsatility index above the 95th percentile for GA [38].
Early and late neonatal sepsis	Early neonatal sepsis was diagnosed by the onset of signs and associated positive culture at or before 72 hours of life. Late neonatal sepsis was diagnosed by the onset of clinical signs consistent with sepsis after 72 hours of life. The isolation of pathogenic bacteria from a positive blood culture was the "gold standard" for diagnosis. In cases without positive blood culture, neonatal sepsis was diagnosed in presence of clinical signs associated with laboratory markers [34, 39].
RDS	Defined according to the European Consensus Guidelines on the management of RDS [40].
Severity of BPD	Classified according to the oxygen requirement at 36 weeks postmenstrual age: • mild, if on room air at 36 weeks or discharge; • moderate, if $FiO_2 < 0.30$ at 36 weeks or discharge; • severe, if $FiO_2 > 0.30$ and/or positive pressure ventilation or nCPAP at 36 weeks or discharge [41].
NEC	Diagnosed and staged by the criteria of Bell [42]. We only considered NEC with grade 2A or higher.
Acute renal failure	Defined as a sudden decline in kidney function resulting in imbalance of fluids and electrolytes and in an increase in blood concentration of urea and creatinine (> 1.5 mg/dL) [43, 44].
Retinopathy of prematurity	Classified according to the International Classification [45].
IVH	Staged according to Papile. Only stages III and IV were analyzed [46].
hs-PDA	Diagnosed on the basis of echocardiographic features [47].
Cystic periventricular leukomalacia	Classified according to de Vries [44].

BPD: bronchopulmonary dysplasia; GA: gestational age; hs-PDA: hemodynamically significant patent ductus arteriosus; IVH: intraventricular hemorrhage; NEC: necrotizing enterocolitis; RDS: respiratory distress syndrome; SGA: small for gestational age.

standard charts of the World Health Organization were used to characterize postnatal growth failure (< 10th percentile) at 12 and 24 months [18].

We also collected data regarding the duration of parenteral nutrition (PN) as well as the day of start of fortified oral feeding. Breastfeeding was promoted and recommended as soon as the preterm neonate acquired tolerance. In neonates with BPD, we used restriction of liquids in the order of 120-140 mL/kg/day associated with modular caloric supplements or enteral hypercaloric nutrition [19, 20].

Days of hospitalization, weight, length, HC and respiratory comorbidities, medication at discharge, social and familiar characteristics were collected, too.

All subjects were immunized with palivizumab and pneumococcal vaccine.

Statistical analysis was performed using SPSS®, version 25. Categorical variables were analyzed by absolute and relative frequencies and continuous variables were analyzed according to their distribution by mean (± standard deviation) for symmetric distribution or median (minimum-maximum) for asymmetric distribution. Categorical variables were evaluated by Chi square or Fisher's exact test and continuous variables by independent t-test or Mann-Whitney U test. Risk factors associated with poor growth were evaluated by a multivariate analysis using logistic regression. A p-value below 0.05 was considered statistically significant.

Results

A total of 90 preterm neonates were enrolled; 51 (56.7%) were female and the median GA was 28 weeks (24-29). In our population, 30 (33.3%) neonates had BPD: 12 (40%) had mild, 4 (13.3%) had moderate and 14 (46.7%) had severe BPD.

Tab. 2 summarizes demographic, maternal, gestational and delivery data among cases and controls.

The anthropometric measures of the cases were significantly smaller than the controls; the group of controls had an average GA of 2 weeks higher and an average weight of about 200 g greater (**Tab. 2**).

Tab. 3 shows clinical characteristics and management during hospitalization. The total number of days on supplemental oxygen was associated with BPD (OR = 1.22, 95% CI [1.02-1.46], p = 0.026), as expected.

Data regarding social and familiar characteristics, respiratory comorbidities and medication of the population are shown in **Tab. 4**. Regarding respiratory comorbidities, there were no significant differences in the two groups, something that would not be expected.

Tab. 5 shows anthropometric measures in the first 2 years of life and **Tab. 6** shows postnatal growth failure at 12 and 24 months of corrected age. At 12 months, 89% of neonates with BPD were below the 10th centile for length as were 71% for weight and 53% for HC (p = 0.036, p = 0.006, p = 0.001, respectively).

Tab. 7 identifies the risk factors for growth in BPD neonates at 12 months of corrected age.

GA and pre-pregnancy mother's weight were shown to be associated with short stature (OR = 0.042, 95% CI [0.004-0.470], and OR = 0.892, 95% CI [0.779-0.967], respectively). Weight at birth was also associated with low weight and HC growth (OR = 0.895, 95% CI [0.800-0.921], and OR = 0.880, 95% CI [0.872-0.980], respectively).

Figures 1, **2** and **3** present the mean length, weight and HC during the first 2 years of life.

Discussion

This study was elaborated to evaluate the length, weight and HC growth of preterm infants with BPD during their first 2 years of life compared with healthy preterm infants.

At birth, neonates with BPD have a significantly lower GA and lower mean length, weight and HC than the control group. This is a limitation of a retrospective study knowing that the group of controls has an average GA of 2 weeks higher and an average weight of 200 g greater.

At discharge, neonates with BPD had a significantly higher mean length, weight and HC, as shown in **Tab. 5** and **Figures 1**, **2** and **3**. One possible explanation is that neonates with BPD are hospitalized for a longer time in neonatal units and have higher postmenstrual age at discharge when compared with healthy neonates (40 weeks versus 36.5 weeks, respectively). Moreover, preterm neonates with BPD are deficient in reserves acquired mainly by placental transfer in the third trimester of gestation and so they need more energy and protein intake during the first weeks of life. Our NICU follows the rules established by the Portuguese Society of Neonatology. If our preterm neonates have an insufficient caloric intake, modular caloric supplements (maltodextrin or medium-chain triglycerides) are used. In case of a persistent poor weight evolution, enteric or

Table 2. Comparison of demographic, maternal, gestational and delivery data among cases of bronchopulmonary dysplasia (BPD) and controls.

		Total (n = 90)	Cases (n = 30)	Controls (n = 60)	p-value
Gender	Male	39 (43.3)	16 (53.3)	23 (38.3)	0.176 [a]
	Female	51 (56.7)	14 (46.7)	37 (61.7)	
GA (weeks), median (min-max)		28 (24-29)	27 (24-29)	29 (26-29)	**< 0.001** [d]
Birth weight (grams), mean (± SD)		1,005.02 (222.74)	885.33 (197.84)	1,064.87 (211.37)	**< 0.001** [c]
Length at birth (cm), mean (± SD)		35.28 (3.68)	33.02 (3.23)	36.36 (3.41)	**< 0.001** [c]
HC at birth (cm), mean (± SD)		25.58 (2.05)	24.46 (1.72)	26.12 (1.99)	**< 0.001** [c]
SGA		4 (4.4)	2 (6.7)	2 (3.3)	0.469 [a]
Maternal age, mean (± SD)		32.78 (5.87)	32.07 (4.05)	33.13 (6.6)	0.347 [c]
Maternal higher education		48 (56.5)	16 (57.1)	32 (56.1)	0.930 [a]
Maternal employment	Employed	70 (79.5)	22 (78.6)	48 (80)	0.877 [a]
	Unemployed	18 (20,5)	6 (21.4)	12 (20)	
Pre-pregnancy mother's weight, median (min-max)		69 (48-120)	65.5 (48-114)	70 (48-120)	0.937 [d]
BMI prior to pregnancy ≥ 30		14 (16.7)	5 (17.9)	9 (16.1)	0.836 [a]
Weight gain, mean (± SD)		8.25 (4.36)	7.54 (4.74)	8.62 (4.15)	0.319 [c]
Previous gestations		55 (61.1)	19 (63.3)	36 (60)	0.760 [a]
Multiple gestation		26 (28.9)	10 (33.3)	16 (26.7)	0.511 [a]
Antenatal corticosteroids		85 (97.7)	27 (93.1)	58 (100)	0.109 [b]
Full cycle of antenatal corticosteroids		50 (70.4)	19 (76)	31 (67.4)	0.448 [a]
Complications during pregnancy	Clinical chorioamnionitis	17 (18.9)	6 (20)	11 (18.3)	0.849 [a]
	Gestational diabetes	6 (6.7)	4 (13.3)	2 (3.3)	0.093 [b]
	Pre-eclampsia	24 (26.7)	10 (33.3)	14 (23.3)	0.312 [a]
	HELLP syndrome	8 (8.9)	5 (16.7)	3 (5)	0.111 [b]
	Abruptio placentae	19 (21.1)	5 (16.7)	14 (23.3)	0.465 [a]
	Prolonged rupture of membranes	25 (27.8)	6 (20)	19 (31.7)	0.244 [a]
	FGR	16 (17.8)	6 (20)	10 (16.7)	0.697 [a]
	Abnormal umbilical blood flow	14 (15.6)	8 (26.7)	6 (10)	**0.040** [a]
	Oligoamnios	11 (12.2)	1 (3.3)	10 (16.7)	0.063 [b]
	Hydramnios	3 (3.3)	2 (6.7)	1 (1.7)	0.257 [b]
Chronic maternal pathology prior to pregnancy	Diabetes	1 (1.1)	1 (3.3)	0	0.333 [b]
	Chronic arterial hypertension	15 (16.7)	9 (30)	6 (10)	**0.016** [a]
Smoking during pregnancy		13 (14.4)	6 (20)	7 (11.7)	0.289 [a]
Type of delivery	C-section	61 (67.8)	23 (76.7)	38 (63.3)	0.202 [a]
Apgar score	1st minute Apgar score < 7	47 (52.2)	21 (70)	26 (43.3)	**0.017** [a]
	5th minute Apgar score < 7	16 (17.8)	11 (36.7)	5 (8.3)	**0.001** [a]
Delivery room management	Resuscitation with endotracheal tube	22 (24.4)	12 (40)	10 (16.7)	**0.015** [a]
Placental histology	Chorioamnionitis	55 (61.1)	15 (50)	40 (66.7)	0.126 [a]

Data are presented as n (%) if not otherwise indicated.
[a] Chi square test; [b] Fisher's exact test; [c] Independent t-test; [d] Mann Whitney U test.
BMI: body mass index; FGR: fetal growth restriction; GA: gestational age; HC: head circumference; HELLP syndrome: hemolysis, elevated liver enzyme levels and low platelet levels; SGA: small for gestational age.

parenteral nutrition is used as quickly as possible [19, 20].

Several authors, such as Embleton et al., describe that early initiation of parenteral nutrition is beneficial and will reduce the energy and protein deficit associated with difficulty in maintaining a total nutrient intake [21]. In our study, we assessed parenteral nutrition and, by analyzing **Tab. 3**, we were able to verify that the days of parenteral nutrition were higher in cases than controls. So, at discharge, the difference in weight in the two groups can be justified by using these enriched formulas and parenteral nutrition for longer periods in newborns with BPD [22].

Table 3. Clinical characteristics and management during hospitalization among cases of bronchopulmonary dysplasia (BPD) and controls.

		Total (n = 90)	Cases (n = 30)	Controls (n = 60)	p-value
RDS		72 (80)	29 (96.7)	43 (71.7)	**0.005** [b]
Surfactant administration		70 (77.8)	27 (90)	43 (71.7)	0.063 [a]
Number of doses, median (min-max)		1 (1-5)	2 (1-5)	1 (1-3)	0.125 [c]
First dose of surfactant (minutes of life), median (min-max)		43.5 (4-1,320)	42 (10-300)	45 (4-1,320)	**0.001** [c]
Supplemental oxygen	**Maximum FiO_2, median (min-max)**	0.35 (0.21-1)	0.45 (0.21-1)	0.30 (0.21-1)	0.051 [c]
	Total number of days, median (min-max)	21 (1-148)	64.5 (18-148)	4 (1-52)	**< 0.001** [c]
Mechanical ventilation	**Non-invasive (nCPAP)**	90 (100)	30 (100)	60 (100)	-
	Number of days, median (min-max)	34 (3-63)	42 (3-63)	32 (4-60)	**0.010** [c]
	Invasive	63 (70)	30 (100)	33 (55)	**< 0.001** [b]
	Number of days, median (min-max)	11 (1-76)	27 (1-76)	4 (1-25)	**< 0.001** [c]
Vasoactive amines		14 (15.6)	8 (26.7)	6 (10)	**0.040** [a]
Treatment	**Systemic and inhaled corticosteroids**	18 (20)	17 (56.7)	1 (1.7)	**< 0.001** [b]
	Inhaled bronchodilators	16 (17.8)	15 (50)	1 (1.7)	**< 0.001** [b]
	Diuretics	9 (10)	9 (30)	0	**< 0.001** [b]
Pneumonia		11 (12.2)	8 (26.7)	3 (5)	**0.005** [a]
Early sepsis (≤ 72 h)		5 (5.6)	2 (6.7)	3 (5)	0.879 [b]
Late sepsis (> 72 h)		41 (45.6)	21 (70)	20 (33.3)	**0.001** [a]
Meningitis		2 (2.2)	0	2 (3.3)	0.551 [b]
NEC (grade ≥ 2A Bell)		8 (8.9)	1 (3.3)	7 (11.7)	0.261 [b]
Transient acute renal failure		12 (13.3)	7 (23.3)	5 (8.3)	**0.048** [a]
ROP stage ≥ 2		13 (68.4)	11 (68.8)	2 (66.7)	0.898 [b]
IVH ≥ 3		13 (14.4)	7 (23.3)	6 (10)	0.090 [a]
Hydrocephalus with periventricular derivation		7 (7.8)	3 (10)	4 (6.7)	0.682 [b]
cPVL		7 (7.8)	3 (10)	4 (6.7)	0.682 [b]
hs-PDA		41 (45.6)	21 (70)	20 (33.3)	**0.001** [a]
Days of PN, median (min-max)		25 (3-79)	36.5 (11-79)	21 (3-76)	**0.001** [c]
Day of start of oral feeding, median (min-max)		30 (10-88)	40 (12-85)	23 (10-88)	**0.002** [c]
Stay in NICU (days), median (min-max)		65 (26-148)	84.5 (47-148)	57.5 (26-124)	**< 0.001** [c]
Corrected aged at discharge (weeks), median (min-max)		37 (35-49)	40 (36-49)	36.5 (35-45)	**< 0.001** [c]
Medication at discharge	**Oxygen**	7 (7.8)	7 (23.3)	0	**< 0.001** [b]
	Inhaled corticosteroids	13 (14.6)	13 (44.8)	0	**< 0.001** [b]
	Diuretics	1 (1.1)	1 (3.4)	0	0.326 [b]
	Inhaled beta 2 agonists	4 (4.5)	4 (13.8)	0	**0.010** [b]

Data are presented as n (%) if not otherwise indicated.
[a] Chi square test; [b] Fisher's exact test; [c] Mann Whitney U test.
cPVL: cystic periventricular leukomalacia; FiO_2: fraction of inspired oxygen; hs-PDA: hemodynamically significant patent ductus arteriosus; IVH: intraventricular hemorrhage; nCPAP: nasal continuous positive airway pressure; NEC: necrotizing enterocolitis; NICU: Neonatal Intensive Care Unit; PN: parental nutrition; RDS: respiratory distress syndrome; ROP: retinopathy of prematurity.

Although they increased in length, weight and HC, they had significantly lower values at 12 months than healthy preterm infants of the same age, as shown in **Tab. 5** and **Figures 1**, **2** and **3**. We explored the association of BPD with growth failure in a multivariate logistic regression model and, after adjustment, GA was associated with length growth, which is consistent with the findings of Sakurai et al. [23]. In our study, preterm neonates with BPD had lower GAs than healthy preterm (**Tab. 2**). Lower GA strongly influences energy and nutritional deficiencies, which have an impact on the neonate's growth [23]. In addition, we must not forget that genetic potential may have a great influence on adult height [9].

It is important to note that growth depends not only on individual factors but also on environmental factors, such as maternal age,

Table 4. Social, familiar characteristics, respiratory comorbidities and medication in first 2 years of life among cases of bronchopulmonary dysplasia (BPD) and controls.

		Total (n = 90)	Cases (n = 30)	Controls (n = 60)	p-value
Number of people in the household, median (min-max)		4 (2-8)	3.5 (3-5)	4 (2-8)	0.724 [c]
Preschool aged siblings		31 (34.4)	11 (36.7)	20 (33.3)	0.754 [a]
Nursery during the first 2 years of life		27 (33.8)	5 (16.7)	22 (44)	**0.012** [a]
Respiratory comorbidities	**Pneumonia**	12 (17.9)	4 (16)	8 (19)	0.898 [b]
	Episode of bronchospasm	8 (11.9)	4 (16)	4 (9.5)	0.459 [b]
	Bronchiolitis	41 (61.2)	12 (48)	29 (69)	0.087 [a]
	URI	33 (49.3)	13 (52)	20 (47.6)	0.729 [a]
Medication	**Bronchodilators**	39 (88.6)	10 (66.7)	29 (100)	**0.003** [b]
	Systemic corticosteroids	3 (30)	0	3 (100)	**0.008** [b]
	Inhaled corticosteroids	18 (81.8)	9 (69.2)	9 (100)	0.115 [b]

Data are presented as n (%) if not otherwise indicated.
[a] Chi square test; [b] Fisher's exact test; [c] Mann Whitney U test.
URI: upper respiratory tract infection.

Table 5. Anthropometric measures in the first 2 years of life among cases of bronchopulmonary dysplasia (BPD) and controls.

		Cases (n = 30)	Controls (n = 60)	p-value
At discharge	**Length, cm**	45.04 (2.32)	43.06 (2.46)	**0.001** [a]
	Weight, grams	2,520.90 (393.23)	2,166.29 (444.36)	**< 0.001** [a]
	HC, cm	33.57 (1.49)	32.23 (1.91)	**0.001** [a]
At 3 months of corrected age	**Length, cm**	49.19 (2.96)	49.20 (3.31)	0.998 [a]
	Weight, grams	3,451 (529.83)	3,562.93 (708.35)	0.448 [a]
	HC, cm	36.46 (1.37)	36.41 (2.20)	0.904 [a]
At 6 months of corrected age	**Length, cm**	57.86 (3.32)	58.83 (3.37)	0.202 [a]
	Weight, grams	5,301.17 (974.39)	5,735.42 (878.2)	**0.036** [a]
	HC, cm	40.11 (1.58)	41.03 (1.70)	**0.017** [a]
At 12 months of corrected age	**Length, cm**	68.24 (3.16)	70.25 (3.95)	**0.020** [a]
	Weight, grams	7,519.64 (1,187.2)	8,318 (1,257.66)	**0.006** [a]
	HC, cm	44.25 (1.64)	45.20 (1.72)	**0.017** [a]
At 18 months of corrected age	**Length, cm**	76.70 (4.33)	76.67 (3.86)	0.978 [a]
	Weight, grams	9,392.88 (1,673.72)	9,776.98 (1,426.28)	0.292 [a]
	HC, cm	46.36 (1.23)	46.9 (1.72)	0.170 [a]
At 24 months of corrected age	**Length, cm**	83.88 (4.03)	83.56 (3.84)	0.739 [a]
	Weight, grams	11,178.2 (1,697.22)	11,152.25 (1,473.13)	0.946 [a]
	HC, cm	47.87 (1.67)	48.12 (1.79)	0.572 [a]

Data are presented as mean (± SD).
[a] Independent t test.
HC: head circumference.

Table 6. Postnatal growth failure at 12 and 24 months of corrected age among cases of bronchopulmonary dysplasia (BPD) and controls.

		Total (n = 90)	Cases (n = 30)	Controls (n = 60)	p-value
At 12 months of corrected age	**Length < P10**	64 (73.6)	25 (89.3)	39 (66.1)	**0.036** [b]
	Weight < P10	44 (50)	20 (71.4)	24 (40)	**0.006** [a]
	HC < P10	26 (29.9)	15 (53.6)	11 (18.6)	**0.001** [a]
At 24 months of corrected age	**Length < P10**	37 (50)	15 (60)	22 (44.9)	0.219 [a]
	Weight < P10	19 (25)	6 (24)	13 (25.5)	0.888 [a]
	HC < P10	8 (11)	3 (12.5)	5 (10.2)	0.768 [a]

Data are presented as n (%).
[a] Chi square test; [b] Fisher's exact test.
HC: head circumference.

Table 7. Risk factors for growth in bronchopulmonary dysplasia (BPD) neonates at 12 months corrected age – multivariate analyses.

		OR	95% CI	p-value
Length < P10	**GA**	0.042 [a]	0.004-0.470	**0.018**
	Pre-pregnancy mother's weight	0.892 [a]	0.779-0.967	**0.008**
Weight < P10	**Weight at birth**	0.895 [b]	0.800-0.921	**0.002**
HC < P10	**Weight at birth**	0.880 [c]	0.872-0.980	**0.030**

[a] Adjusted for weight gain, FGR, tobacco smoking, length and weight at birth, oxygen therapy and corticosteroids at discharge; [b] adjusted for GA, pre-pregnancy weight, weight gain, BMI prior to pregnancy ≥ 30 kg/m^2, gestational diabetes, maternal diabetes, oxygen therapy and corticosteroids at discharge; [c] adjusted for GA, HC at birth, IVH, hydrocephalus with periventricular derivation, cPVL, oxygen therapy and corticosteroids at discharge. BMI: body mass index; cPVL: cystic periventricular leukomalacia; FGR: fetal growth restriction; GA: gestational age; HC: head circumference; IVH: intraventricular hemorrhage.

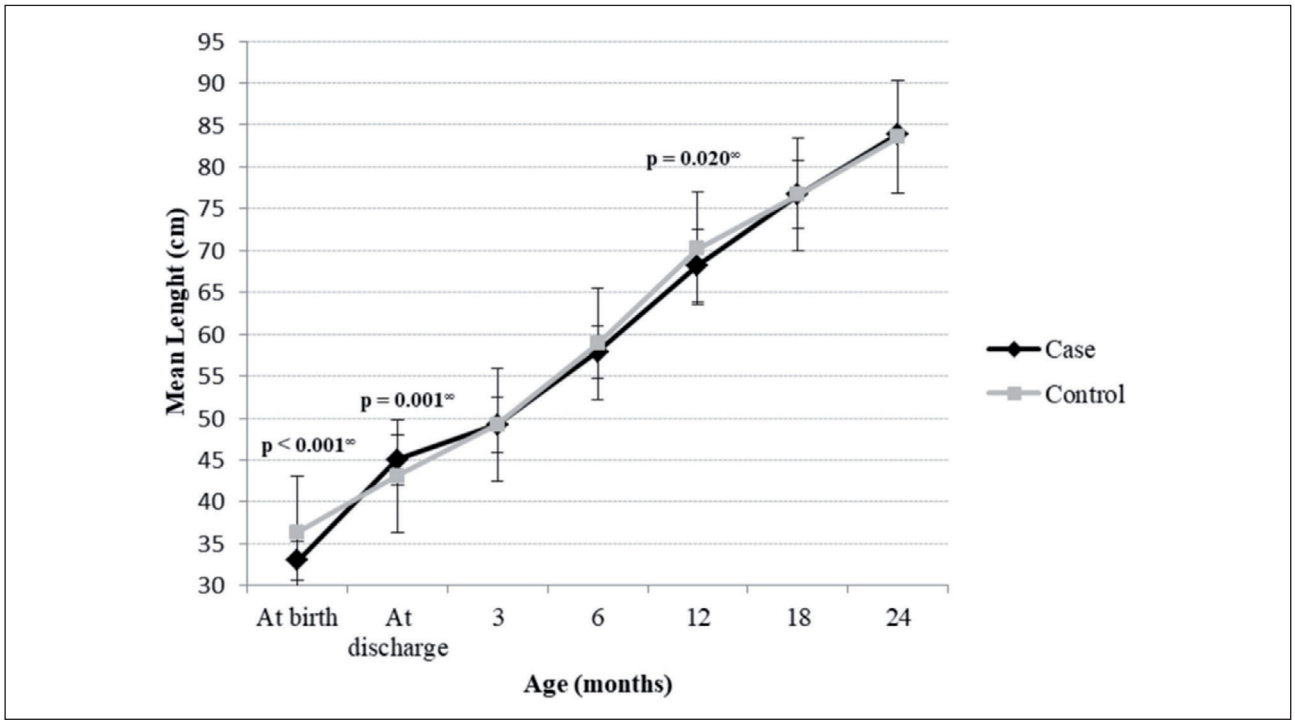

Figure 1. Length in neonates with and without bronchopulmonary dysplasia (BPD).
∞ Independent t-test.

maternal education or employment. In our study, there are no statistically significant differences in these factors. However, pre-pregnancy mother's weight was shown to be associated with length growth and it could be understood as an indicator of environmental conditions and energetic situations during pregnancy. This result was similar to those of Polzlberger et al., who described an association between pre-pregnancy weight status and femur length and front-occipital diameter in the second trimester [24]. As some studies indicate, a low maternal weight is related to poor maternal nutrition and it may have consequences not only in low birth weight but also on children's structural deficit [24]. Fetal growth depends on the maintenance of a healthy intrauterine environment and nutritional support provided by the placenta. This is dependent not only on uteroplacental blood flow, but also on the nutritional status of the mother [25].

Weight at birth was associated with lower weight and HC growth. In our study, neonates with BPD had lower birth weight than healthy neonates (**Tab. 2**) and at the end of the first year of life they still had a lower weight. In fact, lower weight at birth may bring several complications, namely difficulty in combating infections with more re-hospitalizations, in gaining weight or in catching-up HC measurements [26]. As Hack et al. argued, neonates with very low birth weight growth poorly, have smaller HC and a have greater difficulty in having adequate neurologic and psychomotor development [27]. In addition and as described by Ford et al., very low birth weight will have

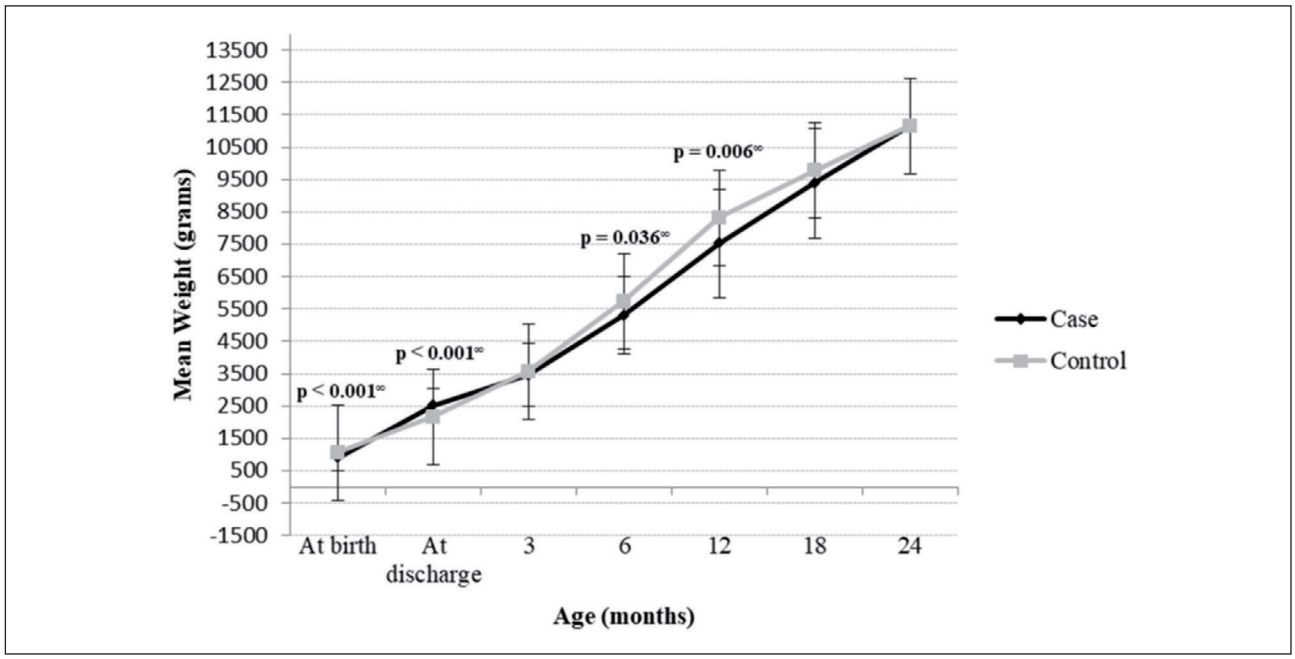

Figure 2. Weight in neonates with and without bronchopulmonary dysplasia (BPD).
∞ Independent t-test.

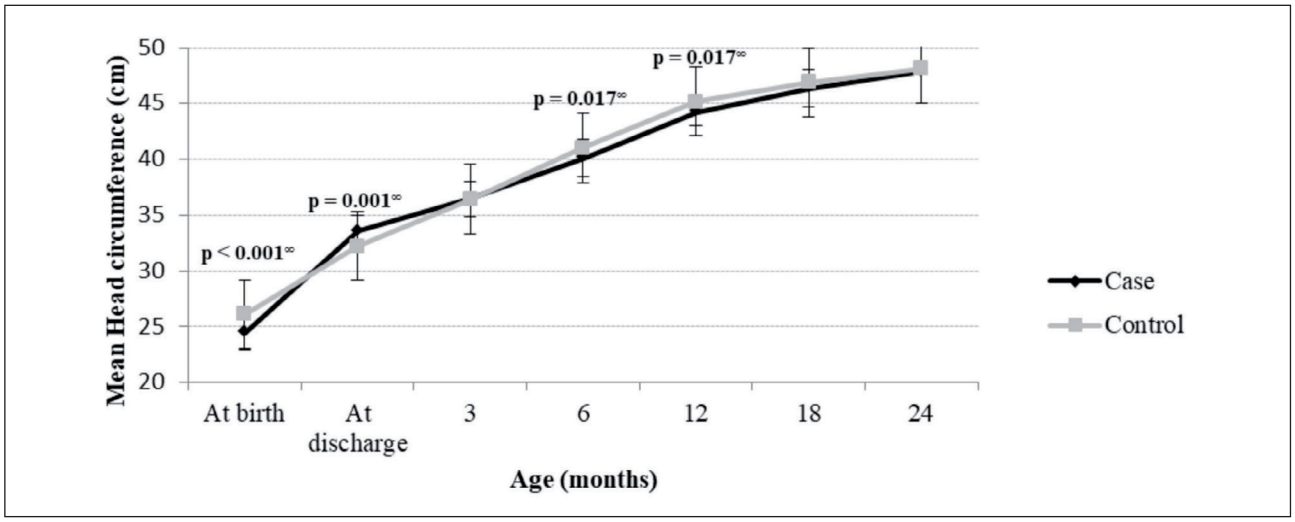

Figure 3. Head circumference in neonates with and without bronchopulmonary dysplasia (BPD).
∞ Independent t-test.

consequences not only in the first years of life but also in adolescence. They reported that newborns with very low birth weight were significantly shorter and had smaller HC than newborns with normal birth weight [28].

At 12 months after term, there were no differences within the growth assessment, a result not according to Huysman et al. [11]. Our study concluded that growth after 12 months in infants with BPD was sufficient to achieve catch-up and so the incidence of growth failure diminished with increasing age. In fact, at 12 months, there are still differences between the two groups. So, catch-up growth occurred after 12 months, possibly between 12 and 18 months.

It is important to note that, although there was a significant difference in GA between the two groups, BPD patients achieved catch-up growth. We can infer that if the difference in GA was smaller, catch-up might occur even before the first year of life. At 24 months, no statistical model was associated with short stature, low weight or low HC, as expected. Neonates with BPD had already achieved catch-up growth.

Regarding respiratory comorbidities, there were no significant differences in the two groups,

something that would not be expected, because the preterm neonates with BPD have more respiratory symptoms, readmissions and use of inhaled medications [29, 30]. One possible explanation would be the small sample size and the fact that it was a retrospective study.

This study has strengths. It was developed in a Level III NICU, a referral center for maternal and neonatal pathology. Furthermore, we used a homogeneous population (with GA less than 30 weeks), both for cases and controls, which facilitated the comparison of the two groups. However, we recognize its limitations. It was a retrospective and observational study with a relatively small sample size. The results cannot be generalized, because it was performed in a single center. More prospective and multicenter studies are needed to evaluate the individual influence of each one of the comorbidities in preterm neonates with BPD.

Conclusions

BPD is a frequent concern in the NICU that affects the growth of preterm neonates. It is essential to know the risk factors involved and how they affect the development of preterm neonates. Our study was able to show that growth between 12 and 18 months of life in preterm infants with BPD was sufficient to catch-up, which probably can be related to better clinical practices in our center.

Declaration of interest

The Authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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