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ORIGINAL ARTICLE

Epidemiological factors involved in the development of bronchopulmonary dysplasia in very low birth-weight preterm infants

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ABSTRACT

BACKGROUND: In spite of the advances made in perinatal medicine, the incidence of bronchopulmonary dysplasia (BPD) has not decreased and the aetiopathogenesis of the "new" BPD is still a matter for debate. The objectives of the present study were to analyse the epidemiological factors and morbidity associated with the development of BPD in a cohort of very low birth-weight (VLBW) preterm infants.

METHOD: This retrospective observational study included all the preterm infants with birth weight ≤1500 g who were admitted to a tertiary-level hospital NICU from 2008 to 2011. A neurological follow-up was also carried out during the first two years of life.

RESULTS: A total of 140 VLBW infants were analyzed: 28.4% presented oxygen dependence at 28 days, and 17.2% at 36 weeks adjusted gestational age. Predictive factors for the development of BPD were gestational age, birth weight, number of days of parenteral nutrition, number of days to achieve full enteral feeding, number of transfusions, duration of respiratory support and insulin administration, vasoactive drugs, diuretics, sedoanalgesia and postnatal corticosteroids. The neonatal morbidity associated with the development of BPD was late neonatal sepsis, patent ductus arteriosus, retinopathy of prematurity (ROP) and intraventricular hemorrhage. Non-significant associations with neurodevelopmental impairment were observed.

CONCLUSIONS: Predictive factors for the development of BPD were respiratory support, feeding and different types of medication. Moreover, patients with BPD had a higher associated morbidity than those who did not develop BPD.

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Key words: Bronchopulmonary dysplasia - Premature birth - Very low birth weight infant - Risk factors.

Bronchopulmonary dysplasia (BPD) is the most common chronic illness and one of the main long-term consequences of preterm births. In the United States, it affects approximately 14,000 very low birth-weight (VLBW) preterm infants every year.[1, 2] Despite important perinatal advances that have been made, the incidence of BPD is not decreasing.[3] Furthermore, it varies widely, due to differences in diagnostic criteria, among other reasons. Thus, according to the Vermont Oxford Network, in 2010 BPD rates ranged from 12% to 32% in newborn infants of less than 32 weeks' gestational age (GA).[4]

Improvements in survival rates of VLBW infants have changed the framework of BPD, which is usually related to the oxygen therapy provided, toward a milder form of the disease, which some authors [5, 6] term "new BPD". This latter form is more related to pulmonary im-

maturity, alveolarization disorders, dysmorphic capillary configuration and/or variable interstitial cellularity and fibroproliferation. There are reasons to believe that the risk factors associated with new BPD are different from the classical ones, although aspects of the aetiopathogenesis of the new disease are still subject to debate. Thus, controversies remain as to the influence or relation of factors such as chorioamnionitis (CA),[7] preeclampsia,[8] persistent ductus arteriosus (PDA) [9] and retinopathy of prematurity (ROP) [10] in the development of BPD.

The benefits of identifying risk factors for BPD in VLBW infants include access to prognostic information and the possibility of determining which infants will benefit from preventive strategies. Advances such as this will enable further improvements in BPD outcomes.

This study has the following main objectives: 1) to analyse the epidemiological factors for BPD development in a cohort of preterm infants with birth weight of less than 1500 g; 2) to analyse the morbidity associated with BPD in our cohort; 3) to study the neurodevelopmental disorders in our cohort of patients during the first two years of life and their relation between these disorders and the development of BPD.

Materials and methods

An epidemiological, observational, and retrospective study was carried out, including all the preterm infants with birth weight ≤1500 g who were admitted to the neonatal intensive care unit of the San Cecilio Clinical Hospital (a tertiary-level hospital) in Granada, Spain, between 1 January 2008 and 21 December 2011. The following exclusion criteria were applied: detectable fetal and/or newborn malformation, genetic syndrome and/or metabolic disorders. Medical records of every patient and data corresponding to the neurological follow-up at the hospital's Early Care Unit at 2, 6, 9, 12, 15-18 and 24 months corrected age were analyzed. The study was approved by the hospital's Ethics Committee.

Definition and variables

The BPD diagnostic criteria used were as described by Jobe and Bancalari, validated by the National Institutes of Health consensus definition.[11]

The variables analyzed were divided into three groups:

1) Pre- and post-natal factors: preeclampsia, clinical maternal chorioamnionitis (presence of fever, leukocytosis or increased C-reactive protein, prenatal corticosteroids, birth weight, small for gestational age (birth weight <p3), gestational age, number of days of mechanical ventilation (MV), number of days of oxygen therapy, number of days of non-invasive mechanical ventilation (NIMV), number of days of parenteral nutrition (PN), number of days from start of enteral feeding (EF) until full enteral feeding (FEF), sodium disorders (hypo-hypernatremia), hypocalcaemia and medication used: number of surfactant doses, number of transfusions (concentrate of red blood cells, concentrate of platelets and/or fresh frozen plasma), insulin (if hyperglycemia with glycosuria persists despite reduced glucose contributions), vasoactive drugs (dopamine/dobutamine for arterial hypotension, increased cardiac output or renal perfusion), caffeine citrate (for apnea provoked by prematurity treatment), sedoanalgesia (*i.e.*, the administration of fentanyl (1 μg/kg/dose) or midazolam (0.1 mg/kg/dose) in the context of the intubation, suctioning the endotracheal tube, central line, MV, etc.), postnatal systemic corticosteroids and systemic diuretics.

2) Morbidity: hyaline membrane disease (HMD), determined by radiological classification [12], pneumothorax, necrotizing enterocolitis (NEC), neonatal sepsis, intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), PDA and its treatment.

3) Neurological follow-up: carried out at the hospital's Early Care Unit, staffed by a neonatologist, a neuropediatrician, a psychologist, a physiotherapist and a social worker. Controls were performed at 2, 6, 9, 12, 15-18 and 24 months' corrected age. Bayley-2, Brunet-Lezine and Haizea-Llevant scales were used. The following study variables were included: mo-

tor impairment (mild neuromotor disorder, *i.e.*, slight asymmetry, diparesis, hemiparesis and tetraparesis), hearing sensory disorder (sensorineural deafness), visual sensory disorder (myopia, vision loss or strabismus), multideficiency (severe intellectual impairment associated with more or less serious motor impairments or sensory or behavioral alterations); conduct disorder (autism or autism spectrum) and psychomotor/cognitive retardation (mild, moderate or severe development immaturity).

Statistical analysis

SPSS Statistics v.15.0 software was used. After the descriptive analysis of the study variables, Student's *t*-test (for the quantitative variables) and the χ^2 test (for the qualitative variables) were applied. Multinomial logistic regression analysis was used to evaluate the relationship between BPD and the different risk factors, adjusting for gestational age, sepsis, PDA and NEC. The results are expressed as odds ratios and the associated 95% confidence interval (CI); $P<0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 149 preterm infants with birth weight ≤1500 g were registered at the NICU during the study period, although we were only able to access 140 electronic medical records. The average GA was 28.7 weeks (standard deviation [SD] 2.2) and the average birth weight was 1120.8 g (SD 279.4) (Table I). Of these

TABLE I.—*Analysis for perinatal and morbidity variables.*

Variable Mean (SD) or N. (%)	No BPD (N.=69)	Mild BPD (N.=35)	Moderate BPD (N.=16)	Severe BPD (N.=9)	P*
GE (weeks)	30.1 (1.5)	27.9 (1.7)	28.1 (1.9)	27.1 (2.0)	<0.001
Birth weight (g)	1279 (231)	1088 (178)	950 (202)	836 (130)	<0.001
SGA (yes/no)	22 (32)	6 (17)	8 (50)	4 (44)	NS
IMV (days)	1.5 (2.9)	10.1 (13.3)	12.1 (15.3)	53.3 (26.3)	<0.001
NIMV (days)	3.2 (3.7)	9.2 (6.8)	13.1 (8.2)	16.1 (10.1)	NS
Oxygen therapy (days)	11.3 (10.6)	44.7 (12.3)	71.6 (36.6)	188.3 (205)	<0.001
Parenteral nutrition (days)	8.5 (7.2)	20.5 (12.3)	24.1 (11.1)	48.9 (22.7)	<0.001
Beginning of EF (days)	2.1 (1.8)	4.9 (5.0)	4.4 (2.3)	9.0 (6.1)	<0.001
Full EF (days)	12.1 (8.5)	23.6 (13.7)	29.4 (15.1)	51.5 (31.1)	<0.001
Surfactant (yes/no)	14 (20)	19 (54)	10 (63)	6 (67)	<0.001
Transfusions	0.8 (1.1)	2.9 (3.1)	3.0 (1.6)	10.4 (5.9)	<0.001
Preeclampsia (yes/no)	26 (38)	11 (31)	6 (38)	4 (44)	NS
Chorioamnionitis (yes/no)	3 (4)	3 (9)	1 (6)	3 (33)	<0.01
Prenatal corticosteroids (yes/no)	54 (78)	31 (89)	14 (88)	6 (67)	NS
Postnatal corticosteroids (yes/no)	5 (7)	6 (17)	6 (38)	9 (100)	<0.001
Pneumotorax (yes/no)	3 (5)	1 (3)	1 (7)	2 (25)	NS
Insulin administration (yes/no)	2 (3)	6 (17)	6 (38)	4 (44)	<0.001
Hypo/hypernatremia (yes/no)	3 (4)	4 (12)	4 (25)	8 (89)	<0.001
Hypocalcemia (yes/no)	3 (5)	8 (24)	8 (13)	2 (25)	<0.001
Late sepsis (yes/no)	14 (20)	20 (57)	6 (38)	6 (67)	<0.001
Vasoactive drugs (yes/no)	16 (24)	24 (71)	14 (93)	7 (88)	<0.001
Sedoanalgesia (yes/no)	9 (13)	14 (40)	16 (10)	9 (100)	<0.001
Diuretics (yes/no)	5 (8)	13 (38)	10 (67)	7 (88)	<0.001
Ductus persistent (yes/no)	9 (13)	9 (26)	4 (25)	7 (78)	<0.001
NEC (yes/no)	11 (16)	10 (29)	3 (19)	1 (11)	NS
HMD (yes/no)	38 (57)	30 (91)	15 (94)	7 (100)	<0.001
IVH (yes/no)	8 (12)	7 (20)	4 (25)	5 (56)	<0.05
ROP (yes/no)	15 (23)	17 (53)	7 (47)	7 (100)	<0.001

GE: gestational age; SGA: small for gestational age; IMV: invasive mechanical ventilation; NIMV: non-invasive mechanical ventilation; EF: enteral feeding; FEF: full enteral feeding; HMD: hyaline membrane disease; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; ROP: retinopathy of prematurity; IVH: intraventricular hemorrhage.
*ANOVA and χ^2 test.

infants, 53 were extremely low birth weight (ELBW).

Neurological follow-up was only possible in 109 cases, due to the absence of follow-up, transfer to another hospital or death.

The BPD prevalence in our sample was most frequent for the mild grade (28.4%) followed by moderate (11.2%) and severe (6%). The descriptive analysis of the different variables included in the study is summarized in Table I.

Prenatal factors

According to our results, preeclampsia, maternal chorioamnionitis and lung maturation are not associated with BPD development (Table I).

Neonatal factors

As shown in Tables I and II, both GA and birth weight were significantly different between patients with and without BPD. Our results show that the higher the number of days with MV (invasive MV or NIMV) or with oxygen therapy, the greater the risk of BPD, and that this could be severe. Multinomial logistic regression analysis showed that the association between number of surfactant doses and BPD is clearly indicative of confounding variable, because the number of surfactant doses is related to the degree of severity of HMD (Tables I, II).

With respect to nutrition, there were significant differences between the duration of PN, number of days from the start of EF until full EF and BPD development (Tables I, II).

There were significant differences in the number of transfusions between patients with and without BPD and between the different grades of BPD (Tables I, II).

With regard to the fluid electrolyte imbalance, our analyses showed that the alterations of sodium levels (especially hyponatremia) and calcium (mainly hypocalcemia) were sig-

TABLE II.—*Multinomial logistic regression analysis for different BPD grades (dependent variable) adjusted for GA, sepsis, PDA and NEC.*

Variable	Mild BPD (N.=35) OR (95% CI)	Moderate BPD (N.=16) OR (95% CI)	Severe BPD (N.=9) OR (95% CI)
GE (w)	0.53 (0.39-0.72)†	0.51 (0.35-0.74)†	0.43 (0.24-0.78)†
Weight (grammes)	0.99 (0.99-1.01)	0.99 (0.98-0.99)†	0.98 (0.97-0.99)†
Chorioamnionitis (yes/no)	1.64 (0.35-7.74)	0.85 (0.17-4.11)	0.58 (0.10-3.40)
MV (days)	1.21 (1.07-1.36)†	1.24 (1.09-1.39)†	1.38 (1.20-1.60)†
Oxygen therapy (days)	1.18 (1.04-1.35)†	1.33 (1.20-1.48)†	1.35 (1.21-1.50)†
NIMV (days)	1.18 (1.04-1.35)*	1.33 (1.15-1.55)†	1.28 (1.09-1.51)§
PN (days)	1.21 (1.04-1.20)§	1.18 (1.08-1.28)†	1.28 (1.12-1.45)†
Beginning of EF (days)	1.18 (0.90-1.55)	1.15 (0.86-1.54)	1.94 (0.99-3.80)
Full EF (days)	1.09 (1.01-1.17)*	1.18 (1.08-1.29)†	1.25 (1.11-1.41)†
Transfusions (n)	2.06 (1.30-3.22)§	2.19 (1.36-3.55)§	3.22 (1.88-5.55)†
EPO (yes/no)	2.75 (0.96-7.90)	4.60 (1.19-17-81)*	0.32 (0.02-4.25)
Surfactant (doses)	1.70 (0.57-5.06)	2.96 (0.76-11.6)	1.67 (0.28-9.82)
HMD (yes/no)	3.23 (0.77-13-43)	5.54 (0.64-48)	–
Pneumothorax (yes/no)	0.46 (0.04-5.76)	1.28 (0.10-16.1)	3.90 (0.27-55.4)
Hypocalcemia (yes/no)	4.07 (0.80-20.5)	1.89 (0.23-15.1)	3.91 (0.37-41.1)
Hypo/hypernatremia (yes/no)	1.46 (0.25-8.48)	3.99 (0.65-24-4)	–
Insulin (yes/no)	3.06 (0.47-20.0)	9.94 (1.44-68.6)*	6.09 (0.41-89.5)
Prenatal corticosteroids (yes/no)	2.32 (0.55-9.67)	1.68 (0.29-9.70)	0.76 (0.10-5.56)
Postnatal corticosteroids (yes/no)	1.68 (0.34-8.29)	8.97 (1.52-53.0)*	–
Diuretics (yes/no)	3.25 (0.84-12.6)	16.9 (3.21-89.3)§	17.7 (1.47-213)*
Adrenergic drugs (yes/no)	4.89 (1.68-14.2)§	32.8 (3.8-283)§	22.0 (1.90-254)*
Sedoanalgesia (yes/no)	1.68 (0.47-5.97)	2.04 (0.43-9.60)	21.5 (1.7-271)*

GE: gestational age; MV: mechanical ventilation; NIMV: non-invasive mechanical ventilation; PN: parenteral nutrition; EF: enteral feeding; EPO: erythropoietin; HMD: hyaline membrane disease.
*P<0.05; §P<0.01; †P<0.001.

nificantly more common among patients with BPD (Tables I, II).

The use of insulin, in response to prolonged hyperglycemia, is associated with the moderate BPD (Table II).

Patients with BPD needed vasoactive drugs more frequently than those without it, and the difference was statistically significant (Tables I, II).

The use of sedoanalgesia was associated with a greater risk of severe BPD (Table II), which we assume to be related to a greater duration of MV and to delayed extubation.

Regarding the medication used for BPD treatment, diuretics were significantly associated with moderate and severe BPD (Table II). However, there was no association with bronchodilators, and corticosteroids were only associated with moderate BPD.

Morbidity

As shown in Table I, most patients with severe BPD had suffered HMD. However, after adjusting for GA, late sepsis, persistent ductus and NEC (variables that are often associated with BPD), no association was observed between BPD and HMD. Neither was the existence of pneumothorax associated with BPD (Table II).

NEC did not differ significantly between patients with and without BPD, but there was an association between IVH and BPD (OR=9.5; 95% CI: 2.11-43). ROP was associated with BPD (OR=3.7; 95% CI: 1.5-9.1). Late sepsis was associated with BPD (OR=18.3; 95% CI: 2.1-155), as was PDA (OR=23; 95% CI: 4.1-130).

Neurodevelopmental impairment

Among the ELBW infants, slight motor disorder was observed in seven patients, diparesis in three, hemiparesia in two and tetraparesis in one. The infants with a birth weight ≥1000 g presented slight motor disorder in four cases, diparesis in one, hemiparesis in three and tetraparesis in two. Auditory sensory disorder was observed in nine patients with ELBW and in four with birth weight ≥1000 g. Among the ELBW patients, mild cognitive delay was observed in 61 cases and moderate delay in four, while those with a birth weight ≥1000 g presented mild cognitive delay in 16 cases and moderate delay in seven. Behavioral disorders were only observed in five of the ELBW infants. Multiple disorders were observed in three infants with ELBW and in two with a birth weight ≥1000 g. No clinically significant associations were observed between BPD, in any degree, and neurodevelopmental impairment (Table III).

Discussion

According to our results, the predictive factors for BPD development are GA, birth weight, duration of respiratory support and parenteral nutrition, time to reach full EF, number of transfusions, and the need for medication (insulin, vasoactive drugs, sedoanalgesia and diuretics). The neonatal morbidity factors associated with the development of BPD were late neonatal sepsis, PDA, HIV and ROP. The presence of NEC has been associated with a delay in the withdrawal of ventilator support

TABLE III.—*Multinomial logistic regression analysis of the neurodevelopmental impairments (dependent variable) for different BPD grades, adjusted for GA, sepsis, PDA and NEC.*

Variable	Mild BPD (N.=35) OR (95% CI)	Moderate BPD (N.=16) OR (95% CI)	Severe BPD (N.=9) OR (95% CI)
Visual sensory disorder	0.20 (0.05-0.81)	0.44 (0.08-2.47)	0.09 (0.01-1.39)
Hearing sensory disorder	1.64 (0.31-8.46)	1.30 (0.20-8.47)	0.51 (0.02-12.7)
Psychomotor retardation (yes/no)	6.99 (1.52-32.0)*	4.25 (0.77-23.5)	0.1 (0.01-10.5)
Conduct disorder (yes/no)	1.17 (0.15-9.31)	1.14 (0.09-14.2)	–
Multideficiency	1.35 (0.07-26.6)	0.70 (0.03-14.7)	0.17 (0.01-8.61)
Motor impairments	0.60 (0.19-1.92)	1.91 (0.53-6.88)	9.34 (0.91-95.5)

*P<0.05.

and with BPD.[13] In our study sample, no association was observed between BPD, in any degree, and NEC.

The prevalence of BPD in our sample was similar to that reported in other studies conducted in Spain,[14] although some authors have reported a lower prevalence than in our case.[15, 16]

Maternal-obstetric factors

Although preeclampsia and maternal chorioamnionitis (CA) have been widely studied in this field, their association with BPD remains controversial.[17, 18] In the case of CA, this inconsistency can be attributed to differences in population, method, definition (clinical/histological CA) and confounding factors considered. The histological evidence of CA (chorion inflammation, amnion and placenta) is the gold standard because cases can be asymptomatic and reflect chronic infection. In our sample, CA was observed more frequently in cases of severe BPD.

Neonatal factors

In most studies, gestational age and weight are considered as two independent risk factors for BPD.[15, 19, 20] In consequence, the results obtained in the present study are in line with those described elsewhere.

Nutrition plays an important role in lung development and maturation. Malnutrition is known to interfere with pulmonary defence against hyperoxia, volutrauma and infection, affecting lung development, maturity and repair. In our study sample, if full enteral nutrition was not achieved in 12 days (the average period recorded for patients without BPD) the risk of BPD was higher (Table II). To the best of our knowledge, no previous study has associated the number of days of parenteral nutrition, the time required to achieve full enteral feeding and BPD development.

As shown in the Results section, the greater the duration of respiratory support, the higher the risk of developing BPD. In this respect, there were few discrepancies between previous studies,[21] which is not surprising because this is a well-known risk factor for BPD.

Inflammation is considered the most important factor in the pathogenesis of BPD, and the role of corticosteroids as anti-inflammatory agents has been extensively documented. In general, it is strongly recommended to avoid the use of postnatal corticosteroids during the first week of life because the benefits obtained from early treatment to prevent BPD do not counteract the potential adverse effects of this treatment.[22, 23] On the other hand, diuretics have traditionally been used in the treatment of BPD because alveolar interstitial edema, which decreases pulmonary compliance, is commonly present in BPD. In our study, the use of postnatal corticosteroids was associated with moderate BPD, because corticosteroid treatment is usually indicated for newborn infants when there is difficulty in withdrawing MV. In this respect, similar results have been reported by Richard *et al*.[4] The use of diuretics was significantly associated with all grades of BPD.

Morbidity

Infection is another classical risk factor for the development of BPD. Landry *et al*.[24] and Gagliardi *et al*.[21] considered sepsis to be a risk factor for BPD. Our results reflect the same association. Another classical risk factor for BPD is PDA. Many studies have reported the existence of an association between PDA and BPD,[24-30] and all reflect a clear association between increased mean fluid intake during the first week of life, PDA and BPD.[31]

Free radicals are known to be involved in the pathogenesis of certain diseases of prematurity such as BPD, ROP, IVH and NEC and it has been suggested that there might exist an association between them. The ROP prevalence recorded at our hospital has decreased in recent years,[32] and this may be a relevant factor in our search for associations with BPD. Such an association has been reported in several papers,[28, 33, 34] but others have failed to confirm this.[35, 36] In the present study, we observed 100% of cases of ROP in patients with

severe BPD, due to their greater dependence on oxygen. However, we found no evidence of a predominance of NEC in patients with BPD, in contrast to the results obtained by Leviton *et al*.[37]

Neurodevelopmental impairment

Most studies analysing the influence of BPD on neurodevelopmental impairment in VLBW infants have a cross sectional design. In consequence, the independent effect of this pathology on neurological development is difficult to evaluate, because of the high possibility of additional medical complications. Nevertheless, although preterm infants are at greater risk of neurodevelopmental disorders, BPD seems to be an additional risk factor, which is not associated with a specific disorder of neuropsychological development, but with a more general one. Various papers have suggested that BPD is a predictive factor of NDI during the infant's first two years of life.[35-38] Corroborating earlier findings,[38] we observed no significant association between NDI and BPD, at any grade, after adjusting the regression analysis for gestational age, late sepsis, persistent ductus and NEC (Table III).

Our study reveals the existence of an association between BPD and little-known factors in this respect, such as sedoanalgesia, vasoactive drugs and insulin. We also describe a neurologic follow up conducted during the first two years of life, which enabled us to analyze the neurodevelopmental disorders that affect patients with BPD, and to determine the association between these aspects. Among the limitations of our study, it is important to note that it was conducted retrospectively. In view of the number of variables, a larger sample size could have enabled an interesting alternative approach to be taken.

Conclusions

According to the results obtained in this study, the predictive factors for the development of BPD are respiratory support, the type of feeding and the different types of inotropic medication. Patients with BPD had a higher associated morbidity than those who did not develop the disease.

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