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Outcomes of extremely low birth weight infants with bronchopulmonary dysplasia: Impact of the physiologic definition ☆

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ABSTRACT

Aims: We compared neurodevelopmental outcomes of extremely low birth weight (ELBW) infants with and without bronchopulmonary dysplasia (BPD), using the physiologic definition.
Study design: ELBW (birth weights < 1000 g) infants admitted to the Neonatal Research Network centers and hospitalized at 36 weeks postmenstrual age (n = 1189) were classified using the physiologic definition of BPD. Infants underwent Bayley III assessment at 18–22 months corrected age. Multivariable logistic regression was used to determine the association between physiologic BPD and cognitive impairment (score < 70).
Results: BPD by the physiologic definition was diagnosed in 603 (52%) infants, 537 of whom were mechanically ventilated or on $FiO_2 > 30\%$ and 66 who failed the room air challenge. Infants on room air (n = 505) and those who passed the room air challenge (n = 51) were classified as "no BPD" (n = 556). At follow up, infants with BPD had significantly lower mean weight and head circumference. Moderate to severe cerebral palsy (7 vs. 2.1%) and spastic diplegia (7.8 vs. 4.1%) and quadriplegia (3.9 vs. 0.9%) phenotypes as well as cognitive (12.8 vs. 4.6%) and language scores < 70 (24.2 vs. 12.3%) were significantly more frequent in those with BPD compared to those without BPD. BPD was independently associated (adjusted OR 2.4; 95% CI 1.40–4.13) with cognitive impairment.
Conclusions: Rates of adverse neurodevelopmental outcomes in early childhood were significantly higher in those with BPD. BPD by the physiologic definition was independently associated with cognitive impairment using Bayley Scales III. These findings have implications for targeted post-discharge surveillance and early intervention.

1. Introduction

Bronchopulmonary dysplasia (BPD) is a serious morbidity among preterm infants, with a reported incidence of 42% among infants 501–750 g birth weight and 25% among those with 751–1000 g birth weight [1]. Traditional BPD, defined as supplemental oxygen (O_2) administration at 36 weeks postmenstrual age was diagnosed in 42% of a recent cohort of preterm infants 22 to 28 weeks gestation from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NICHD NRN) who survived to 36 weeks postmenstrual age [2]. BPD is associated with an increased risk of neurodevelopmental impairment with mental, psychomotor and language delays in early childhood [3, 4]. At school age, children with BPD have greater risk of growth retardation and academic difficulties [5, 6].

The diagnosis of BPD has evolved in recent years from that based solely on duration of O_2 administration to one incorporating a standardized assessment of O_2 need. The traditional definition of BPD is based on O_2 administration at a postnatal age of 28 days or

Abbreviations: BPD, Bronchopulmonary dysplasia; NICHD, National Institute of Child Health and Development; NRN, Neonatal Research Network; RDS, Respiratory distress syndrome; ROP, Retinopathy of prematurity; NEC, Necrotizing enterocolitis; PVL, Periventricular leukomalacia.

☆ For the Generic Database Subcommittee of the *Eunice Kennedy Shriver* NICHD Neonatal Research Network.

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postmenstrual age of 36 weeks. The National Institutes of Health (NIH) consensus definition of BPD includes a classification of severity (mild, moderate and severe) based on O_2 use at 28 days and at 36 weeks postmenstrual age or discharge home for preterm infants<32 weeks gestation [7]. The predictive validity of the NIH consensus definition for 18 month outcomes has been demonstrated by Ehrenkranz et al. in the NICHD NRN in a large cohort of extremely low birth weight (ELBW) infants born between 1995 and 1999 [8]. The incidence of any neurodevelopmental impairment, cerebral palsy, mental and psychomotor developmental indices of <70 on the Bayley Scales of Infant Development II and blindness and hearing impairment significantly increased as the severity of BPD increased. In another study, compared with children with mild or moderate BPD, those with severe BPD perform poorly on IQ tests at 3 years and had lower performance IQs and poorer perceptual organization at 8 years of age [9]. In both these studies, moderate BPD was based on FiO_2<30% at 36 weeks postmenstrual age, an imperfect definition due to disparate individual and center practices related to target O_2 saturations and thresholds for O_2 therapy.

The physiologic definition of BPD, developed by Walsh et al., is based on a standardized assessment of O_2 saturation during a timed stepwise reduction of administered O_2 to room air, with clearly defined criteria for 'passing' or 'failing' the challenge [10]. It has been demonstrated to be feasible, safe and reliable and to reduce the reported rate of BPD in individual centers of the NICHD NRN by a mean of 10% [11]. The relationship between BPD by the physiologic definition and early childhood growth and neurodevelopmental outcomes has not been previously investigated. In this prospective observational cohort study from the NICHD NRN, we compared the growth and neurodevelopmental outcomes at 18–22 months corrected age of a recent cohort of ELBW (birth weights 401–1000 g) infants with and without physiologic BPD. We further examined the association between BPD by the physiologic definition and cognitive impairment on the Bayley Scales III. Our hypothesis was that preterm ELBW infants with BPD by the physiologic definition would have a higher rate of adverse growth and neurodevelopmental outcomes at 18–22 months corrected age, compared to those without BPD by the physiologic definition and that BPD would be an independent predictor of cognitive impairment.

2. Material and methods

This was a secondary analysis of data collected prospectively as part of the NICHD NRN very low birth weight registry (Generic Database) and Follow-up Study. Institutional Review Boards at each participating center approved both the database and follow-up studies.

2.1. Study population

Inclusion criteria consisted of the following: preterm infants with birth weights of 401–1000 g, born between January 1, 2006 and June 30, 2007, eligible for follow-up (<27 weeks gestation and inborn, or in an approved study with follow-up), and still hospitalized at 36 weeks postmenstrual age. Infants were classified as having "physiologic BPD" if they fulfilled either of two conditions: a) any form of assisted ventilation or continuous positive airway pressure (CPAP) or supplemental O_2 with an effective FiO_2>30% at 36 weeks postmenstrual age or b) O_2 via nasal cannula or hood with effective FiO_2<30% and failed the stepwise O_2 reduction challenge in the 36th postmenstrual week, using previously published criteria (O_2 saturation 80% to 89% for 5 consecutive minutes or <80% for 15 s) [11]. The "No physiologic BPD" group comprised infants on room air at 36 weeks postmenstrual age or those who passed the room air challenge, irrespective of clinical O_2 administration.

Data collected included demographic characteristics such as gestational age at birth (by best obstetric estimate), ethnicity, gender and small for gestational age status and clinical data such as 5-minute Apgar score, surfactant therapy, presence of respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC) requiring surgery (modified Bell's stage III), retinopathy of prematurity (ROP), bloodstream infections, severe intracranial hemorrhage (ICH) and cystic periventricular leukomalacia (PVL). Maternal data on antenatal steroids were also obtained. Severe intracranial hemorrhage was defined as blood/echodensity in the cerebral parenchyma or if ventricular enlargement occurred in association with blood/echodensity in the ventricular system (Grade III or IV intracranial hemorrhage). Follow-up information included growth parameters, results of a structured neurologic examination by trained examiners and language and cognitive scores on Bayley Scales of Infant Development III at 18–22 months corrected age. Blindness was defined as no useful function in either eye or possibly blind with some functional vision and deafness as requiring hearing aids in both ears. Moderate to severe cerebral palsy were defined as Gross Motor Functional Classification system level 2 or higher. Maternal education was defined as either less than high school diploma or high school diploma or higher level. Medicaid insurance, defined as public insurance or uninsured was used as surrogate for low socioeconomic status.

2.2. Statistical analysis

Descriptive data were expressed as mean (SD) and number (percent) as appropriate. Data were compared between groups of infants with and without physiologic BPD. Wilcoxon rank-sum tests or t-tests were used for between-group comparisons of continuous data. Categorical data were analyzed using Fisher's exact test or Chi-square test, as appropriate. Multivariable logistic regression analysis was used to determine the association between BPD using the physiologic definition and cognitive impairment (cognitive score<70), after adjusting for confounding variables that have been previously demonstrated to impact developmental outcomes. The basic model included gestational age, male gender, maternal education, and BPD by the physiologic definition. Center as a random effect was not significant. With center in the model, a fitting problem occurred, caused by the scarcity or absence of cases among a number of the centers. In light of its insignificance as a covariate, the decision was made to exclude center from the model. The other factors examined were small for gestational age status, surgical NEC, severe IVH or cystic PVL, bloodstream infection, and antenatal steroids. Because bloodstream infection and antenatal steroids were insignificant and contributed nothing to the model fit, they were dropped from the model. Associations with p value of <0.05 were considered statistically significant.

3. Results

A total of 2716 extremely low birth weight (ELBW) infants were admitted to the centers of the NICHD NRN between January 1, 2006 and June 30, 2007, 2065 of whom were eligible for the follow-up study. Of these, 1189 infants were in the hospital at 36 weeks (725 had died by 36 weeks, 89 had transferred, and 62 had been discharged). Fig. 1 is a flowchart describing the study cohort.

3.1. Short-term outcomes

The vast majority of infants had sufficient data to diagnose physiologic BPD (1159; 97.5%). BPD by the physiologic definition was diagnosed in 603 (52%) infants. A total of 117 (10%) of our cohort underwent the room air challenge, 51 (44%) of whom passed. Table 1 compares the demographic characteristics of ELBW preterm infants with and without BPD by the physiologic definition. Infants with physiologic BPD were significantly more premature and had lower birth weights, were more likely to be male, to have a 5 min Apgar score of <5 and to have less exposure to antenatal steroids