Relationship between severe bronchopulmonary dysplasia and severe retinopathy of prematurity in premature newborns

Jasleen K. Singh, MD,[a] Erica M. Wymore, MD,[b] Brandie D. Wagner, PhD,[c] Tamara S. Thevarajah, MS,[a] Jennifer L. Jung, MD,[a] John P. Kinsella, MD,[b] Alan G. Palestine, MD,[a] and Anne M. Lynch, MB, MSPH[a]

BACKGROUND Bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP) are two adverse sequelae of preterm birth associated with abnormal vascular development. The purpose of this study was to characterize the relationship between these two outcomes at a single institution.

METHODS The medical records of infants screened for ROP at the University of Colorado Hospital between January 2012 and December 2017 were reviewed retrospectively. ROP was classified according to Early Treatment Retinopathy of Prematurity (ET-ROP) criteria; BPD, according to the 2010 Criteria from the National Institute for Child Health and Human Development. We examined the relationship between moderate–severe BPD and the development of severe ROP (type 1 or 2) using univariate analysis and multivariable logistic regression with the odds ratio as a measure of association. Covariates included gestational age and birth weight at delivery.

RESULTS A total of 625 cases were reviewed. Of these, 64 infants (10%) developed severe ROP and 176 (28%) infants developed moderate–severe BPD. We found a significant relationship between these two outcomes following adjustments for gestational age, birth weight, and multiparity (OR = 3.2; 95% CI, 1.6-6.5 [$P < 0.01$]).

CONCLUSIONS In our cohort of preterm infants, we found a significant relationship between moderate–severe BPD with severe ROP. We hypothesize that these two neonatal outcomes have links with a common pathogenesis. (J AAPOS 2019;23:209.e1-4)

Retinopathy of prematurity (ROP) is a prematurity-related ocular complication associated with neovascularization of the retina.[1-3] It occurs specifically in premature infants and is a leading cause of preventable blindness worldwide.[4] The most recent screening guidelines in the United States were published in 2013 and are used in most institutions.[5] Bronchopulmonary dysplasia (BPD), a chronic lung disease, is also found in infants born at a lower gestational age. It is noteworthy that BPD also has links to abnormal pulmonary vascular growth.[6-8] Indeed, a relationship between ROP and BPD has been described by several authors.[9-16] However, many of these studies date back to the 1990s,[9,11] and none of these studies have applied the most recent National Institute of Child Health and Human Development (NICHD) severity classification to the definition of BPD.[17] The purpose of the present study was to determine the relationship between BPD and severe ROP in a contemporary, single-center cohort of infants screened for ROP using the most recent definitions of BPD.

Author affiliations: [a]Departments of Ophthalmology, University of Colorado School of Medicine, Aurora; [b]Department of Pediatrics, Section of Neonatology, University of Colorado School of Medicine, Aurora; [c]Department of Biostatistics and Informatics, Colorado School of Public Health, Aurora

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Correspondence: Jasleen K. Singh, MD, Department of Ophthalmology, University of Colorado School of Medicine, 13123 E. 16th Avenue, B430. Aurora, CO 80045 (email: jasleen.singh@ucdenver.edu).

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Subjects and Methods

This study was approved by the Colorado Multiple Institutional Review Board. A retrospective cohort study was conducted using the records of an ROP registry developed by the Department of Ophthalmology at the University of Colorado School of Medicine. The registry includes detailed information on the neonatal course and the results of the ROP examinations. Quality control on the dataset includes procedures for automatic range checks for numerical data and an annual secondary review of at least 20% of the records.[18-20] Data abstraction and analysis was performed by a

dedicated interdisciplinary team of pediatric ophthalmologists, neonatologists, and a trained research team. Infants were screened at the University of Colorado Hospital between January 2012 and December 2017. Those who did not survive to their first ROP examination were excluded.

Disease Classifications

Ophthalmologists performed ROP screenings, which followed standard guidelines[5,15,21] defined by the International Classification of ROP.[22] ROP was categorized as severe ROP or low-grade/no ROP. Severe ROP was defined as type 1 (stage 1 or 2 ROP in zone I with plus disease, stage 3 zone I with or without plus disease, or stage 2 or 3 ROP in zone II with plus disease) or type 2 ROP (stage 1 or 2 ROP in zone I without plus disease, or stage 3 ROP in zone II). Low-grade ROP was defined as ROP not meeting type 1 or 2 criteria. The indication for treatment with laser photocoagulation was based on the ET-ROP criteria.[2] The treatment indications for use of anti–vascular endothelial growth factor (VEGF) therapy was for stage 3 or plus disease in zone 1.[23]

A neonatologist (EMW) classified all cases of BPD according to the NICHD consensus panel description.[17] In addition, we adjusted for altitude in Aurora, Colorado.[8] In brief, infants were defined as having BPD if they required supplemental oxygen at 28 days of life and had formal oxygen reduction testing at 36 weeks' postconceptual age (PCA) or at discharge, whichever was first. BPD severity was classified as (1) mild (room air or need for <26% oxygen, or discharged home on supplemental oxygen prior to 36 weeks' PCA); (2) moderate (need for >26% to <35% oxygen); or (3) severe (need for >35% oxygen and/or need for positive pressure respiratory support, based on oxygen correction at altitude compared to sea level).[6] For purposes of analysis, BPD was categorized into mild or no BPD (mild/no BPD) and moderate or severe BPD (moderate–severe BPD). Documentation of formal oxygen reduction testing by neonatal intensive care unit (NICU) staff was required for BPD classification. Infants who died prior to 36 weeks' PCA were included in the composite outcome, because it was unknown whether these infants would have developed moderate–severe BPD had they survived, and their exclusion could bias the results. These infants were grouped in the severe BPD category.

Covariates

We examined other covariates in this analysis, including gestational age at delivery, birth weight, race/ethnicity, parity, mode of delivery, and presence of histologic chorioamnionitis.[24]

Statistical Analysis

The relationship of categorical risk factors with neonatal associations and with severe ROP was tested using the χ^2 test ($P < 0.05$). Two-sample t tests were used for differences between continuous variables. We conducted a multivariable logistic regression analysis to determine the adjusted odds ratio of moderate–severe BPD and other neonatal risk factors for severe ROP. Potential confounding variables, those associated with both the ROP outcome and BPD, were included in the regression model. All analyses were performed using SAS software (version 9.4, SAS Institute Inc, Cary, NC).

Results

In our cohort of 625 infants, the mean gestational age (with standard deviation) was 28.9 ± 2.5 weeks, and birth weight was 1121 ± 347 g. The clinical characteristics of our cohort are found in Table 1. We found that 64 infants (10%) developed severe ROP, and 176 (28%) developed moderate–severe BPD. A significant association was found between moderate–severe BPD and severe ROP (concordance between two variables of 77%, $P < 0.001$). Multiparity, gestational age, and birth weight were other significant risk factors associated with severe ROP.

Adjusted for gestational age, birth weight, and multiparity, infants who had moderate–severe BPD had increased odds of developing severe ROP (OR = 3.2; 95% CI, 1.62-6.49 [$P < 0.001$) compared to infants with mild or no BPD.

Discussion

We found an incidence of severe ROP and moderate–severe BPD of 10% and 28%, respectively. Following adjustment for gestational age, birth weight, and multiparity, the odds ratio of moderate–severe BPD for severe ROP was significantly elevated (3.2). As expected, the lower extremes of gestational age and birth weight were significant risk factors for severe ROP.

Other investigators have also evaluated the relationship between any ROP and BPD and other respiratory concerns. Ajayi and colleagues[11] demonstrated that infants with severe BPD were 1.7 times more likely to develop any retinopathy and 1.8 times more likely to develop severe ROP compared with controls using Northway's criteria for BPD.[25] Holmström and colleagues[15] also found a similar relationship (OR = 17) between Northway's definition of BPD and any ROP. The results of our study are in keeping with these earlier studies; however, our study used the contemporary definitions of both ROP and BPD.

It has been suggested that BPD and ROP share a common pathogenesis.[1-3,6-8,26] ROP is believed to have multiple phases, which have links with dysregulation of both neuronal and vascular development of the retina.[1,27,28] There is a prephase of antenatal sensitization via inflammation.[1,27] Phase 1 is retina vascular growth cessation secondary to a higher oxygen environment with downregulation of oxygen-regulated growth factors like VEGF.[1,27] In phase 2, there is retinal neovascularization induced by hypoxia.[1,2,27] In this phase of ROP, the compromised retinal blood vessels cannot supply enough oxygen to the developing retina, which leads to increased metabolic demands of the retina, increased hypoxia-driven local VEGF production, and subsequent retinal

Table 1. Clinical characteristics of study cohort (n = 625)

Risk factor	No. (%)
ROP type	
Type 1	26 (4.1)
Type 2	38 (6.1)
Low grade	110 (17.6)
None	451 (72.2)
BPD type	
None	106 (17.0)
Mild	326 (52.2)
Moderate	36 (5.8)
Severe	140 (22.4)
Other[a]	17 (2.7)
Male	325 (52.0)
GA, weeks, mean ± SD	28.9 ± 2.5
Birth weight, g, mean ± SD	1121 ± 347
Infant ethnicity	
Non-Hispanic white	445 (71.2)
Hispanic	177 (28.3)
Other	3 (0.5)
Baby Race	
White	453 (72.5)
African American	88 (14.1)
Asian	15 (2.4)
Other	69 (11.0)
Multiparous	318 (50.9)
C-section	426 (68.2)
Histologic chorioamnionitis	219 (35.0)

BPD, bronchopulmonary dysplasia; *BW,* birth weight; *GA,* gestational age; *ROP,* retinopathy of prematurity.
[a]Infants who had BPD diagnosis before discharge.

neovascularization.[1] Normal pulmonary development involves a normal angiogenic state for desirable pulmonary vascular growth, which parallels airway branching and adequate alveolarization.[29,30] Expression and signaling of multiple growth factors, particularly VEGF, have been identified as crucial to alveolar structure.[31,32] Disruption of this angiogenic state thus affects both pulmonary vascular development and alveolarization, promoting the progression of BPD. Thus, ROP and BPD both have links to dysfunction of angiogenic signaling pathways, which may explain their association.[1-4,6-8,29-32]

This study has several limitations. Although the major risk factors for ROP (gestational age and birth weight at delivery) were examined as covariates, other risk factors, including our NICU's oxygen saturation policies, were not included in the analysis. We would like to have examined the role of avastin in ROP and BPD; however, the number of infants in our cohort who received avastin was small (n = 5). The ROP registry does not include babies who died before an ROP examination could be performed; these infants are likely the most medically unstable, and their inclusion could have potentially resulted in different estimates of associations between severe ROP and BPD. A major strength of our study was the inclusion of patients using strict and up-to-date definitions of ROP and BPD. Moreover, an interdisciplinary team meticulously collected our data.

Literature Search

PubMed was searched on December 9, 2018, without date restriction, for English-language results, using the following terms: *retinopathy of prematurity* and *bronchopulmonary dysplasia*.

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