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The influence of small for gestational age status on outpatient bronchopulmonary dysplasia outcomes

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Abstract

OBJECTIVE—To describe the characteristics of small for gestational age (SGA) and non-SGA infants with bronchopulmonary dysplasia (BPD) and to ascertain whether respiratory outcomes and health-care utilization patterns in these two populations differ.

STUDY DESIGN—Three hundred and twenty-five infants with BPD born at <32 weeks gestation were recruited in the outpatient setting. Sociodemographic data and indicators of respiratory morbidity were collected via questionnaire and retrospective chart review.

RESULT—SGA infants were on average 1 month older than non-SGA infants at discharge from the neonatal intensive care unit and were more likely to have a weight less than 10th percentile at first clinic visit. History of SGA was associated with increased risk of emergency department visits as well as with caregiver perception of poor weight gain.

CONCLUSION—SGA status in infants with BPD is associated with increased health-care utilization, including length of initial hospitalization and emergency department visits.

INTRODUCTION

Over the past several decades, survival of premature infants and especially that of very low birth weight (VLBW) infants has increased significantly, in turn resulting in an increase in survival rates of infants with bronchopulmonary dysplasia (BPD).[1,2] BPD was first described by Northway *et al.*[3] in 1967 and has classically been defined as supplemental oxygen dependence at 36 weeks postmenstrual age or at 28 days of age.[4] This definition was clarified by the National Institute of Child Health and Human Development (NICHD) in June 2000 workshop, with a severity-based definition classifying BPD as mild, moderate or severe,[5] subsequently validated in a study by Ehrenkranz *et al.*[6]

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Some studies have reported up to a fourfold increase in rates of BPD in small for gestational age (SGA) infants, likely due to *in utero* compromise resulting in impairment in lung function.[7,8] A large population-based study by Lal *et al.*[7] conducted in the United Kingdom found that SGA infants showed a significantly greater risk of developing BPD with odds ratios of 1.34 and 1.87 for the 28 days of age and 36 weeks postmenstrual age definitions, respectively. This study additionally described that SGA premature infants were at a higher risk of death than non-SGA counterparts before reaching either 28 days of age or 36 weeks postmenstrual age.[7]

SGA status has been frequently used as a marker for intrauterine growth restriction (IUGR), even though these terms are not synonymous. Infants with IUGR may not be SGA, and, alternatively, SGA infants may not have been affected by growth restriction.[9] However, SGA status is useful in capturing the majority of IUGR infants, especially when the presence or absence of an *in utero* growth-restricting mechanism cannot be ascertained for an individual patient retrospectively.

Effects of IUGR on developing lung tissue has been well described in animal models, including by Joyce *et al.*,[10] who described impaired gas exchange, reduced lung compliance and increased chest wall compliance in IUGR lambs 8 weeks after birth, with these changes persisting at 2 years after birth.[11] Additionally, Rozance *et al.*[12] described decreased pulmonary alveolarization and vascular growth, as well as pulmonary artery endothelial cell dysfunction *in vitro* in fetal sheep affected by IUGR. Several studies of growth-restricted neonates with BPD reflect these effects of IUGR on developing lung tissue. Bose *et al.*[13] demonstrated that fetal growth restriction, defined as birth weight <1 s.d. below the mean, was an independent risk factor for the development of BPD after adjusting for multiple prenatal and neonatal variables.[13] While fetal growth restriction has been reported in multiple studies as a predictor of BPD, it is unclear how growth restriction or SGA status impacts severity of BPD and overall clinical outcomes once the diagnosis of BPD has been made.

In terms of clinical impact of BPD, previous studies have demonstrated that BPD prolongs the initial length of stay. An observational study by Klinger *et al.*[14] in very low birth weight infants cited an adjusted length of stay of 84.1 days in BPD infants and 58.1 days in infants without the diagnosis. Similar effects are seen with regard to respiratory morbidities, with premature infants with oxygen dependence at discharge or at 36 weeks post-menstrual age being at higher risk for respiratory symptoms such as cough, wheeze and bronchodilator therapy in one study[15] and increased rates of readmission within the first 2 years after birth compared with non-BPD infants in other studies.[16] It is unclear how a history of growth restriction or SGA status contributes to rates of respiratory morbidity after hospital discharge, including rates of readmission, in infants diagnosed with BPD. A better understanding of differences in SGA and non-SGA patients with BPD, with regard to both demographic characteristics and respiratory outcomes, would allow clinicians to tailor management to individual patients and to better counsel families regarding anticipated outcomes.

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To determine whether respiratory outcomes and health-care utilization patterns in the first 2 years of life differed among BPD infants with or without history of SGA status at birth, we conducted a retrospective review of medical records and assessed acute care usage and respiratory symptoms via caregiver questionnaires at outpatient clinic visits. We hypothesized that BPD infants/children who were born SGA would have greater respiratory morbidity compared with infants/children who were not SGA at birth.

METHODS

Study sample

Participants (n = 325) were recruited and consented from the Johns Hopkins Bronchopulmonary Dysplasia Clinic between January 2008 and March 2013. Patients were included if they were accompanied by a consenting parent or caregiver and met the inclusion criteria, which were (1) a diagnosis of BPD by the referring neonatal intensive care unit or staffing pediatric pulmonologist, (2) born at <32 weeks gestation and (3) having clinical data for review before the age of 2 years. This study was approved by the Johns Hopkins University Institutional Review Board (Protocol Number: NA_00051884).

Data collection

Patients' caregivers were asked to complete questionnaires at each clinic encounter. Retrospective chart review of clinic encounters and neonatal intensive care unit admissions was also conducted. Birth weight percentile was derived from published United States norms for gestational ages.[17] SGA was defined as birth weight of less than the 10th percentile, corrected for gestational age. Weight percentile at the first clinic visit was derived from CDC norms and adjusted for gestational age. Median household income was derived using residential zip codes and 2000 United States Census data. Insurance coverage (private or public) was obtained from billing records, and race/ethnicity was self-reported. Inhaled corticosteroid use was defined as any use before age 2 years based on chart review. Diuretic use was defined as taking spironolactone, chlorothiazide and/or furosemide. Gastroesophageal reflux disease medication use was defined as taking H_2 blockers or proton pump inhibitors; motility agent use data was not collected in this study. The presence or absence of gastrostomy tubes and respiratory support were ascertained at the first clinic encounter. Respiratory morbidities were determined via yes/no questions on questionnaires. These included primary outcomes such as emergency department visits, hospital admissions, systemic steroid use and antibiotic use for respiratory indications since the last clinic visit, as well as caregiver perception. Secondary outcomes that were assessed include the presence or absence of difficulty breathing, rescue β-agonist use, activity limitations and nighttime symptoms within 1 week of questionnaire completion. Caregiver perception of weight gain was obtained by the questionnaire. Secondary outcomes were assessed as occurring 0, 1–3 and ≥4 days within the past week, but for the purposes of analysis, these outcomes were dichotomized into occurring or not occurring in the past week.

Data analysis

Statistical methods include Student's t-tests and χ^2 tests for comparing demographic and clinical characteristics between SGA and non-SGA infants. Logistic regression modeling

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was used to generate odds ratios of specific respiratory morbidities occurring with SGA status. As caregivers completed questionnaires at several visits, morbidity outcomes were assessed through generalized estimating equations regression methodology, clustered by subject. Unadjusted and adjusted odds ratios are presented with adjustments including age at the time of questionnaire completion, gestational age and factors that differed between SGA and non-SGA infants, especially weight percentile <10% at first clinic visit and age at the time of discharge from the initial hospitalization. STATA IC 11 (StataCorp LP, College Station, TX, USA) was used for all statistical analysis. *P*-values <0.05 were considered statistically significant.

RESULTS

Demographics

Of the 325 BPD patients included in the study, 9.5% ($n = 31$) had a birth weight less than the 10th percentile for gestational age, qualifying for SGA status (Table 1). Gestational ages ranged from 22 completed weeks to 31 completed weeks. Mean gestational age of the study population was 26.3 weeks, with an s.d. of 2.1, with SGA subjects having a mean gestational age 5 days above that of non-SGA participants (mean ± s.d.: 26.9 ± 2.4 and 26.2 ± 2.1, respectively, $P = 0.07$). Similar to previously published studies on national cohorts of infants with BPD,[18] our population had an over-representation of male infants (58.2% male). The average age at discharge for infants included in this study was 4.3 months. SGA infants had longer hospital stays, with a mean age at discharge 1.0 months greater than that of non-SGA infants ($P = 0.028$). There was no difference between SGA and non-SGA groups with regard to sex, ethnicity, median household income and public insurance status.

The difference in age at first clinic visit between the two groups was not statistically significant, although trending toward SGA infants being older at first clinic visit (Table 2). SGA infants were more likely to have a weight less than 10th percentile for corrected age at the first clinic visit than non-SGA infants (61.3% vs 22.8%, $P<0.001$). There was no difference in gastrostomy tube status (SGA infants with 32.3% vs 20.4%, $P = 0.13$). Among those patients with a G-tube in place, there was no difference with regard to the presence of fundoplication (SGA infants 70.0% vs non-SGA infants 65.0%, $P = 0.76$). At the time of first clinic visit, 37.9% of infants required supplemental oxygen, 64.3% were prescribed diuretic medications and 66.8% were taking medications for gastroesophageal reflux disease. There was no difference between SGA and non-SGA infants with regard to inhaled corticosteroid use before age 2 years or need for supplemental oxygen, diuretic use or gastroesophageal reflux disease medication use.

With regard to respiratory morbidity after hospital discharge, questionnaire data was collected and analyzed by logistic regressions clustered by subject (Table 3). The adjusted model adjusted for age in months at the time of visit, gestational age, age at hospital discharge and weight less than the 10th percentile at first clinic visit. SGA infants were two times as likely to have had an emergency department visit for respiratory symptoms since the last clinic visit as their non-SGA counterparts in the adjusted model (adjusted odds ratio: 2.16, $P = 0.037$). Inadequate weight gain as perceived by the caregiver completing the questionnaire was more likely for SGA infants (adjusted odds ratio: 2.48, $P = 0.048$). No

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significant increase in risk was noted in SGA infants for hospitalization, systemic steroid use and antibiotic use since the last clinic visit, and there was no increased risk of secondary outcomes such as daytime symptoms, rescue medication use, activity limitations and nighttime symptoms.

DISCUSSION

In this study, we examined the respiratory outcomes of children with BPD in the outpatient setting during the first 2 years of life, with respect to SGA status. We found that a high percentage of infants with BPD have a weight less than the 10th percentile, even when correcting for prematurity, at the time of the first clinic visit. Well over half of SGA infants continued to have weights less than the 10th percentile at a visit occurring on average at more than 6 months of age. This finding was supported by increased caregiver perception of inadequate weight gain in the SGA group as compared with the non-SGA group. However, even non-SGA infants had high rates of poor weight gain. Poor growth is one of the more well-described complications associated with both prematurity and BPD, with a recent study by Wang *et al.*[18] describing higher incidences of poorer oxygenation during feeding as well as growth delay in very low birth weightinfants with severe BPD. Our observations support the need for a multidisciplinary approach to the management of BPD to allow for nutritional optimization, enhanced respiratory outcomes and improved developmental outcomes in this vulnerable population.

With regard to health-care utilization, our study demonstrated that the SGA group had a longer initial hospital stay than the non-SGA, resulting in an increased cost for the initial health-care delivery in the neonatal intensive care unit setting. The subset of BPD patients in the neonatal intensive care unit who were SGA may have had more severe respiratory disease in the immediate neonatal period, and also had increased risk for other SGA-associated morbidities, including mortality.[4,19] SGA infants were additionally more likely to have had a respiratory-related emergency department visit since the preceding clinic visit in models adjusted for gestational age. Surprisingly, this did not extend to a greater likelihood of hospitalization or antibiotic and systemic steroid use.

Limitations

Study participants were limited to infants with a pre-existing diagnosis of BPD who had been referred to a pediatric pulmonologist following initial hospital discharge. We may have missed certain infants with milder disease who were not referred by a neonatologist or primary care physician. Conversely, some of the infants with the most severe cases of BPD may not have survived to discharge, and thus to referral. A recent descriptive study by Padula *et al.*[20] detailing short-term outcomes for a large, multicenter cohort of infants with severe BPD born at <32 weeks gestation quoted a 9% mortality rate in infants with severe BPD before discharge. Additionally, travel distance to our institution may have been prohibitive for some families whose infants had been referred. However, the objective of this study was to provide a description of the respiratory outcomes of SGA and non-SGA infants with BPD referred for subspecialty care, and comparable clinics nationwide likely encounter similar obstacles. Questionnaires completed by families relied upon parental or caregiver

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recall of events since last clinic visit or over the course of the preceding week. Existence of multiple caregivers for many of these infants may limit accuracy of some of the responses. Lastly, several of the parameters assessed are subjective in nature, such as trouble breathing and activity limitations.

Future directions

Future prospective studies would allow for stratification of severity and a more detailed comparison of respiratory outcomes in SGA and non-SGA infants with BPD. Additional variables of interest, such as prenatal diagnosis of growth restriction, history of multiple gestation, clinically significant patent ductus arteriosus or pulmonary hypertension, could be analyzed for potential impact on outcomes in SGA and non-SGA populations. This would confirm or add to our initial finding that SGA status in infants with BPD is associated with increased health-care utilization, including length of initial hospitalization and emergency department visits following discharge. These future studies will also allow for improved management and counseling of families regarding prognosis.

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Table 1

Demographic characteristics of non-SGA and SGA infants

	Total (*n* = 325)	BPD only (*n* = 294)	BPD and SGA (*n* = 31)	*P*-value
	Mean ± s.d. (range)			
Sex (% male)	58.2	59.2	48.4	0.25
Race (% non-white)	69.9	69.1	77.4	0.33
Gestational age (weeks)	26.3 ±2.1 (22.7–31.9)	26.2 ±2.1 (22.7–31.9)	26.9 ±2.4 (23.0–31.9)	0.07
Birth weight (g)	860.0 ±315.4 (380–2069)	888.2 ±312.4 (390–2069)	592.4 ±198.7 (380–1160)	<0.001
Birth weight (percentile)	40.8 ±22.9 (1–95)	44.6 ±20.7 (10–95)	5.3 ±2.3 (1–9)	<0.001
Age at discharge (months)	4.3 ±2.4 (0.4–17.1)	4.2 ±2.3 (0.4–17.1)	5.2 ±2.8 (1.6–14.3)	0.028
Median household income (US$ in thousands)	45.9 ±17.4 (11.1–101.4)	45.8 ±17.2 (11.1–101.4)	47.6 ±19.4 (16.1–98.9)	0.58
Public insurance (%)	60.3	60.2	61.3	0.91

Abbreviations: BPD, bronchopulmonary dysplasia; SGA, small for gestational age.

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Table 2

Outpatient clinical characteristics of non-SGA and SGA infants

	Total (*n* = 325)	BPD only (*n* = 294)	BPD and SGA (*n* = 31)	*P*-value
	Mean ± s.d. (range)			
Age				
Age at first clinic visit (months)	6.8 ±3.0 (1.9–18.3)	6.7 ±3.0 (1.9–18.3)	7.6 ±3.2 (3.7–15.0)	0.13
Respiratory parameters				
Home supplemental oxygen at first clinic visit (%)	37.9	37.8	38.7	0.92
ICS before 2 years of age (%)	81.5	81.0	87.1	0.40
Diuretics at first clinic visit (%)	64.3	62.9	77.4	0.11
Gastrointestinal parameters				
Weight percentile at first clinic visit (percentile)	34.6 ±29.0 (1–99)	36.6 ±29.1 (1–99)	15.8 ±20.1 (1–66)	<0.001
Weight <10th percentile at first clinic visit (%)	26.5	22.8	61.3	<0.001
Gastrostomy tube (%)	21.5	20.4	32.3	0.13
Fundoplication (% of those with G-tube)	65.7 (*n* =70)	65.0 (*n* =60)	70.0 (*n* =10)	0.76
GERD medication at first clinic visit (%)	66.8	67.4	61.3	0.50

Abbreviations: BPD, bronchopulmonary dysplasia; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; SGA, small for gestational age.

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Table 3

Questionnaire data for respiratory morbidities during the first 2 years of life

	Number of subjects	Number of questionnaires	Odds ratio for outcome with SGA status (95% CI)	*P*-value
Emergency dept. (for respiratory symptoms)	280	640		
Unadjusted model			1.43 (0.77–2.65)	0.26
Adjusted model			2.16 (1.05–4.48)	0.037
Hospitalization (for respiratory symptoms)	281	639		
Unadjusted model			1.13 (0.44–2.90)	0.80
Adjusted model			2.01 (0.73–5.59)	0.18
Systemic steroids (for respiratory symptoms)	279	633		
Unadjusted model			0.79 (0.34–1.81)	0.58
Adjusted model			1.05 (0.41–2.66)	0.93
Antibiotics (for respiratory symptoms)	281	639		
Unadjusted model			1.08 (0.52–2.21)	0.84
Adjusted model			1.26 (0.59–2.71)	0.55
Caregiver perception of inadequate weight gain	269	598		
Unadjusted model			3.09 (1.42–6.74)	0.005
Adjusted model			2.48 (1.01–6.11)	0.048
Daytime respiratory symptoms	276	615		
Unadjusted model			1.51 (0.62–3.68)	0.36
Adjusted model			1.65 (0.64–4.31)	0.30
Rescue (β-agonist) medication use	275	608		
Unadjusted model			1.00 (0.42–2.40)	1.00
Adjusted model			1.07 (0.41–2.76)	0.89
Activity limitations	269	595		
Unadjusted model			1.07 (0.45–2.54)	0.88
Adjusted model			1.57 (0.58–4.24)	0.37
Nighttime respiratory symptoms	272	611		
Unadjusted model			1.54 (0.73–3.27)	0.26
Adjusted model			1.57 (0.68–3.64)	0.29

Abbreviations: CI, confidence interval; SGA, small for gestational age.

*Odds ratios were generated through logistic regression, clustered by subject as subjects may have had more than one clinic visit before 2 years of age where data were collected. The adjusted model includes age at the time of clinic visit, gestational age, age at the time of discharge from the initial hospitalization and weight percentile <10% at the first clinic visit.