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Neuromotor Outcomes in Infants With Bronchopulmonary Dysplasia

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We examine the neuromotor outcomes of preterm infants with bronchopulmonary dysplasia. Two hundred and nineteen infants (gestational age, ≤32 weeks; birth weight, ≤1500 g) were studied. Neuromotor development was assessed using the Hammersmith Infant Neurological Examination. All potential risk factors associated with neuromotor scores ($P < 0.015$) were included in the generalized linear model (multiple linear regression) to determine if bronchopulmonary dysplasia had an independent relationship with neuromotor scores. Infants with severe bronchopulmonary dysplasia had lower global scores at ages 6 and 12 months. After adjustment for confounding factors, scores of infants with severe bronchopulmonary dysplasia were reduced by 13.2 units, whereas scores for those with periventricular leukomalacia were reduced by 11.1 units, at age 6 months. At age 12 months, scores for those with periventricular leukomalacia were reduced by 11.9 units. Duration of hospital stay reduced scores by 0.1 for each additional day increase in hospital. Bronchopulmonary dysplasia constitutes a major cause of poor neuromotor outcomes at age 6 months, but improvements in motor outcomes occur over time.

Karagianni P, Tsakalidis C, Kyriakidou M, Mitsiakos G, Chatziioanidis H, Porpodi M, Evangeliou A, Nikolaides N. Neuromotor outcomes in infants with bronchopulmonary dysplasia. Pediatr Neurol 2011;44:40-46.

Introduction

Despite advances in the prevention and management of neonatal acute respiratory illness, bronchopulmonary dysplasia persists as a major complication in surviving, very low birth weight infants [1]. Although the introduction of antenatal steroids has reduced the risk of respiratory distress syndrome, bronchopulmonary dysplasia continues to be a frequent long-term problem [2]. On follow-up, bronchopulmonary dysplasia was associated with an increased incidence of neurodevelopmental disability in infancy [3,4], lower pulmonary function, growth retardation, and academic difficulties at school [5,6]. These infants are more likely to encounter serious complications such as infections and intraventricular hemorrhage [7,8]. Because infants with bronchopulmonary dysplasia manifest frequent episodes of hypoxia and desaturation [9-11], these respiratory insufficiencies could increase the risk for brain injury [12,13]. Current approaches to managing infants with developmental disorders emphasize early assessment and intervention [14]. Among the few studies investigating neurodevelopmental outcomes in preterm infants with bronchopulmonary dysplasia before age 1 year [15-17], one revealed no difference at term [16], two reported some deviations at 3 and 10 months of corrected age [15,18], and another reported poor 1-year developmental and clinical outcomes [17]. These reports are difficult to compare because of variations in methodology. Most studies used the classic definition of bronchopulmonary dysplasia, which may not be suitable for the clinical presentation of neonatal lung disease. Previously, the most widely used definition of bronchopulmonary dysplasia included the requirement of oxygen therapy for at least 28 days and radiographic evidence of lung disorders [19]. Until recently, most researchers used this definition, which was dichotomous and did not allow for an examination of how the severity of bronchopulmonary dysplasia might affect outcomes. A new definition of bronchopulmonary dysplasia has been

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Received January 27, 2010; accepted July 21, 2010.

doi:10.1016/j.pediatrneurol.2010.07.008 • 0887-8994/$ - see front matter

advanced that attempts to quantify severity of disease according to the National Institute of Child Health and Human Development/National Heart, Lung, and Blood Institute Workshop criteria [3]. Although the consensus group strongly advocated a change in the definition of bronchopulmonary dysplasia, to our knowledge, only one study has examined the validity of this severity-based definition, using developmental and clinical outcomes at age 1 year [17].

In addition, because the pathology of bronchopulmonary dysplasia has changed from its earliest descriptions with the advent of the "new" bronchopulmonary dysplasia, which is characterized more by alveolar arrest and less by fibrosis [3], survivors are now much smaller and more immature at birth. Because many of these infants were treated with postnatal corticosteroids and exogenous surfactant, compared with infants born in the early 1980s, the results gained from studies of children born more than two decades ago are not pertinent to preterm children born today. Therefore, this study examined neuromotor outcomes during the first year of age in very low birth weight infants who manifested bronchopulmonary dysplasia vs those without bronchopulmonary dysplasia, and sought to determine whether the severity of bronchopulmonary dysplasia could predict poor neuromotor outcomes, beyond the effects of other risk factors. The definition of bronchopulmonary dysplasia by the National Institutes of Health (Bethesda, MD), which includes the milder clinical form of respiratory disease in preterm infants, was used [3].

Patients and Methods

Participants

This study prospectively recruited very low birth weight preterm infants who were born between January 2005 and January 2008 and who received care in our level III neonatal intensive care unit. Permission was obtained from both hospital and university Ethics Committees. Parental permission was received in each case. Selection criteria included a gestational age of ≤32 weeks, a birth weight of ≤1500 g, an absence of congenital or genetic anomalies, and survival at time of discharge. Infants older than 32 weeks of gestation in this weight category were excluded because they represent a population of patients small for their gestational age. Infants were classified as small for gestational age according to the percentiles of Alexander et al. [20]. Gestational age was determined according to the date of most recent menstrual period reported as "normal," as confirmed by sonographic measurement of crown-rump length during the first trimester of pregnancy. Birth weight was measured using an electronic scale. Two hundred and nineteen infants were eligible for the study.

Demographic and Perinatal Data

Several variables were abstracted from medical records: the child's sex, gestational age, birth weight, Apgar score at 5 minutes, exposure to antenatal steroids, mode of delivery, respiratory variables (use of ventilation, duration of oxygen therapy, and need for surfactant administration), patent ductus arteriosus, necrotizing enterocolitis, intraventricular hemorrhage, periventricular leukomalacia, infection, and duration of hospital stay. All 219 infants underwent early cranial ultrasound scans, and underwent a further cranial ultrasound scan at term or at discharge. Scans were assessed by a neonatologist to identify intra-periventricular hemorrhages and periventricular leukomalacia. Term ultrasonograms were classified as "normal" (88%) or "abnormal" if cystic periventricular leukomalacia (2.7%), ventricular dilatation (6.8%), porencephalic cysts (1.8%), or atrophy (0.4%) were present. Oxygen therapy was indicated when oxygen was required to maintain saturation at a level of 88-92%. Bronchopulmonary dysplasia for infants with a gestational age of <32 weeks was graded for its severity according to the consensus definition of the National Institutes of Health. Mild bronchopulmonary dysplasia was defined as a need for supplemental oxygen (O_2) for ≥28 days, but not at 36 weeks of postmenstrual age or discharge. Moderate bronchopulmonary dysplasia was defined as a need for O_2 for ≥28 days plus treatment with <30% O_2 at 36 weeks of postmenstrual age. Severe bronchopulmonary dysplasia was defined as a need for O_2 for ≥28 days plus treatment with ≥30% O_2 or positive pressure (positive pressure ventilation or nasal continuous positive airway pressure) at 36 weeks of postmenstrual age [3].

Measures of Neurologic Outcomes

Infants were scheduled to be examined at 6 and 12 months of corrected age. At these appointments, a Hammersmith Infant Neurological Examination was performed after a standardized physical examination. All neurologic assessments were performed by a neonatologist and a pediatric physiotherapist with previous experience of the Hammersmith Infant Neurological Examination. Examiners were not informed about the infants' medical histories. None of the infants was oxygen-dependant during follow-up examinations. The optimality score was based on the frequency distribution of scores in a low-risk normal term population at ages 12 and 18 months [21,22], and in a cohort of healthy term infants aged 12-32 weeks [23]. The test consists of 26 items assessing cranial nerve function, posture, movements, tone, and reflexes. Each item is scored separately, and scores can be added to achieve a global optimality score. The overall score can range from a minimum of 0 to a maximum of 78. In the normal population, the median global score for age 6 months is 73 (range, 69-76.5), and for age 12 months, the median global score is 73 (range, 63-78). A global score ≥73 is regarded as optimal, and scores below 73 are regarded as suboptimal [21,23].

Statistical Methods

Assumptions of normality were checked using the Kolmogorov-Smirnov test. The t test was used to compare means of continuous variables, and the χ^2 test was used for comparisons of proportions. One-way analysis of variance, followed by Fisher's post hoc procedure, was used to compare means of global scores for levels of bronchopulmonary dysplasia severity. Tests for normality (Kolmogorov-Smirnov test) revealed that parametric methodology could be used for the analysis. An assumption of linearity for severity of bronchopulmonary dysplasia was rejected. Levels of severity for bronchopulmonary dysplasia could not be treated as scores, and bronchopulmonary dysplasia could not be treated as a scale variable.

Post hoc tests revealed that global scores for the group with severe bronchopulmonary dysplasia were significantly different from those in the other three groups. As a result, severity of bronchopulmonary dysplasia was recoded to reflect this fact, and patients with no, mild, and moderate bronchopulmonary dysplasia formed one group, and patients with severe bronchopulmonary dysplasia formed the other group.

The Pearson correlation coefficient was used to assess independent linear relationships between continuous measurements. Multiple linear regression analysis was used to evaluate confounding effects. All potential risk factors associated with neuromotor scores ($P < 0.015$) were selected for inclusion in the generalized linear model (multiple linear regression), to determine if bronchopulmonary dysplasia demonstrated an independent relationship with neuromotor scores. All statistical analyses were performed using SPSS version 17.0 (SPSS, Inc., Chicago, IL). $P < 0.05$ was considered statistically significant.

Results

Perinatal and demographic characteristics of the infants are listed in Table 1. At baseline, 158 infants (72.1%) manifested no bronchopulmonary dysplasia, 38 (17.3%) manifested mild bronchopulmonary dysplasia, 11 (5.0%) manifested moderate bronchopulmonary dysplasia, and 12 (5.4%) manifested severe bronchopulmonary dysplasia. Groups with and without bronchopulmonary dysplasia were significantly different in both gestational age and birth weight (for both, $P < 0.0001$). The mean (± S.D.) gestational age in the group with bronchopulmonary dysplasia was 27.4 (± 1.6) weeks, whereas in the group without bronchopulmonary dysplasia, it was 29.7 (± 1.4) weeks. The mean (± S.D.) birth weight was 925 g (± 208 g) for those with bronchopulmonary dysplasia, and 1198 g (± 191 g) for those without bronchopulmonary dysplasia. At 6-month follow-up, the groups with no, mild, and moderate bronchopulmonary dysplasia were examined at a corrected mean (± S.D.) age of 5.6 (± 1.3) months, whereas the group with severe bronchopulmonary dysplasia was examined at age 5.77 months (± 1.6 months) (P = 0.769). In total, 156 infants (71.2%) received the Hammersmith Infant Neurological Examination (106 with no bronchopulmonary dysplasia, 30 with mild bronchopulmonary dysplasia, 10 with moderate bronchopulmonary dysplasia, and 10 with severe bronchopulmonary dysplasia).

At age 12 months, the groups with no, mild, and moderate bronchopulmonary dysplasia were examined at a corrected mean (± S.D.) age of 11.79 months (± 1.0 months), whereas the group with severe bronchopulmonary dysplasia was examined at age 12.71 months (± 1.2 months) (P = 0.128). In total, 176 (80.3%) received the Hammersmith Infant Neurological Examination (121 with no bronchopulmonary dysplasia, 35 with mild bronchopulmonary dysplasia, 9 with moderate bronchopulmonary dysplasia, and 11 with severe bronchopulmonary dysplasia). Infants from the group with no bronchopulmonary dysplasia were mainly lost to follow-up. Reasons for loss to follow-up included families moving to other cities or countries, and parental refusal to cooperate. Infants who completed the study were not significantly different in terms of gestational age and birth weight, and had incidences of various neonatal diseases comparable to those who were lost to follow-up (Table 2).

Table 1. Perinatal characteristics of infants

	BPD (n = 61)	No BPD (n = 158)	*P* Value
Gestational age*	27.4 (± 1.6)	29.7 (± 1.4)	0.0001
Birth weight*	925 (± 208)	1198 (± 191)	0.0001
Sex (male)†	36 (59.0)	81 (51.2)	NS
SGA†	13 (21.3)	39 (24.6)	NS
Mode of delivery (CS)‡	51 (83.6)	137 (86.7)	NS
Hospital stay (days)*	88 (± 29)	47 (± 15)	0.0001
Apgar scores at 5 minutes*	7.9 (± 0.8)	8 (± 0.7)	0.007
Conception (IVF)†	26 (42.6)	70 (44.3)	NS
Antenatal steroids†	47 (77)	130 (82.2)	NS
Chorioamnionitis†	6 (9.8)	5 (3.1)	NS
Respiratory distress syndrome‡	61 (100)	133 (84)	0.0001
Surfactant administration†	60 (98.3)	134 (84.8)	0.004
Days on O_2*	53 (± 31)	5 (± 6)	0.0001
Days on MV*	10 (0-92)	1 (0-19)	0.0001
Intraventricular hemorrhage (grades I-II)†	14 (22.9)	15 (9.5)	0.039
Intraventricular hemorrhage (grades III-IV)†	4 (6.5)	2 (1.2)	0.026
Periventricular leukomalacia‡	3 (5)	3 (1.9)	NS
Patent ductus arteriosus†	13 (21.3)	11 (6.9)	0.012
Infection†	45 (73.7)	56 (35.4)	0.0001
Necrotizing enterocolitis†	5 (8.1)	6 (3.8)	NS

* *t* test was used. Data are presented as mean (± S.D.).
† χ^2 test was used. Data are presented as n (%).
‡ Data are presented as n (%).

Abbreviations:
BPD = Bronchopulmonary dysplasia
CS = Cesarean section
IVF = In vitro fertilization
MV = Mechanical ventilation
NS = Not significant
SGA = Small for gestational age

Hammersmith Infant Neurologic Examination Testing

Scores for the Hammersmith Infant Neurological Examination are reported for the follow-up sample at 6 and 12 months of corrected age in Figs 1 and 2. At 6 months of corrected age, 16 of 156 infants achieved optimal scores from 73-78, 60 infants attained scores from 64-72, and 80 infants attained scores from 37-63. At 12 months of corrected age, 79 of 176 infants achieved optimal scores from 73-78, 71 infants attained scores from 64-72, and 26 infants attained scores from 31-63 (Table 3). Table 3 summarizes the finding that Hammersmith Infant Neurological Examination scores for the group with severe bronchopulmonary dysplasia were significantly different from the groups with no, mild, and moderate bronchopulmonary dysplasia (significant P values are presented). The regression analysis indicated that significant independent factors and factors at $P < 0.015$ that potentially influenced the global score at 6 months of corrected age included severe bronchopulmonary dysplasia ($P < 0.001$), gestational age ($P = 0.036$), birth weight ($P = 0.016$), duration of hospital stay ($P < 0.001$), days of oxygen use ($P < 0.001$), days of mechanical ventilation ($P = 0.02$), patent ductus arteriosus ($P = 0.001$), and periventricular leukomalacia ($P = 0.004$). Those statistically significant factors were selected for a further evaluation of interactions between factors. Severe bronchopulmonary dysplasia ($P = 0.016$), periventricular leukomalacia ($P = 0.013$), and mechanical ventilation ($P = 0.033$) significantly influenced the Hammersmith Infant Neurological Examination score. Finally, a model was fit including only these factors, in which only severe bronchopulmonary dysplasia ($P < 0.0001$) and periventricular leukomalacia ($P = 0.011$) were retained. Severe bronchopulmonary dysplasia reduced the global score by 13.2 units, whereas periventricular leukomalacia reduced the

Table 2. Perinatal characteristics of infants assessed or not assessed during follow-up

	Assessed (n = 191)	Not Assessed (n = 28)	*P* Value
Gestational age*	29.1 (1.8)	29.2 (1.6)	NS
Birth weight*	1116 (230)	1163 (234)	NS
Sex (male)†	101 (52.8)	16 (57.1)	NS
Small for gestational age†	46 (24.0)	6 (21.4)	NS
Mode of delivery (CS)†	168 (87.9)	20 (71.4)	0.04
Infection†	85 (44.5)	16 (57.1)	NS
APGAR scores at 5 minutes*	8.1 (0.7)	8.2 (0.6)	NS
Conception (IVF)†	82 (42.9)	14 (50)	NS
Antenatal steroids†	155 (81.1)	22 (78.5)	NS
Respiratory distress syndrome†	167 (87.4)	27 (96.4)	NS
Bronchopulmonary dysplasia†	56 (29.3)	5 (17.8)	NS
None + mild + moderate†	180 (94.2)	26 (92.8)	NS
Severe†	11 (5.7)	2 (7.1)	NS
Intraventricular hemorrhage (grades I-II)	24 (12.5)	5 (17.8)	NS
Intraventricular hemorrhage (grades III-IV) †	6 (3.1)	0	NS
Periventricular leukomalacia†	6 (3.1)	0	NS
Patent ductus arteriosus†	21 (10.9)	3 (10.7)	NS
Necrotizing enterocolitis†	11 (5.7)	0	NS
Days on O_2*	19.5 (27.9)	15.5 (25.4)	NS
Days on MV*	7.3 9 (18.0)	7.0 (14.1)	NS
Hospital stay (days)*	59.6 (27.6)	52.9 (24.8)	NS

* *t* test was used. Data are presented as mean (± S.D.).
† χ^2 test was used. Data are presented as n (%).

Abbreviations:
CS = Cesarean section
IVF = In vitro fertilization
MV = Mechanical ventilation
NS = Not significant

global score by 11.1 units. We thus conclude that after adjusting for all other possible confounders, severe bronchopulmonary dysplasia significantly influences the Hammersmith Infant Neurological Examination score at 6 months of corrected age.

At 12 months of corrected age, a similar analysis was used. Significant independent factors and factors at $P < 0.015$ that potentially influenced the global score at 12 months of corrected age included severe bronchopulmonary dysplasia, duration of hospital stay, days of oxygen use, intraventricular hemorrhage (grades III-IV), and periventricular leukomalacia ($P < 0.001$ for all). Gestational age ($P = 0.125$), mechanical ventilation ($P = 0.057$), and patent ductus arteriosus ($P = 0.079$) were also considered in the initial model. All significant variables were entered into the multiple linear regression model as a first step. Periventricular leukomalacia ($P < 0.0001$) and days of hospital stay ($P < 0.003$) were the only factors retained in the model. Periventricular leukomalacia reduced the global score by 11.9 units, whereas duration of hospital stay reduced the global score by 0.1 unit for each further day in hospital stay. Therefore, severe bronchopulmonary dysplasia was removed from the analysis, and does not seem to influence the global score at 12 months of corrected age.

Discussion

According to this study, infants with severe bronchopulmonary dysplasia, compared with infants with no, mild, and moderate bronchopulmonary dysplasia, attained lower neurologic scores at 6 and 12 months of corrected age After adjustment for confounding factors, severe bronchopulmonary dysplasia exerted an independent adverse effect on global scores at 6 months of corrected age, but did not influence global scores at 12 months of corrected age. Our findings indicate that severe bronchopulmonary dysplasia predicts poor neuromotor outcomes at 6 months corrected age and not during the first year of age. Moreover, infants with periventricular leukomalacia demonstrated a decline in global scores at both 6 and 12 months of corrected age.

Our findings are not consistent with those of Jeng et al., who concluded that bronchopulmonary dysplasia predicts poor developmental and clinical outcomes in very low birth

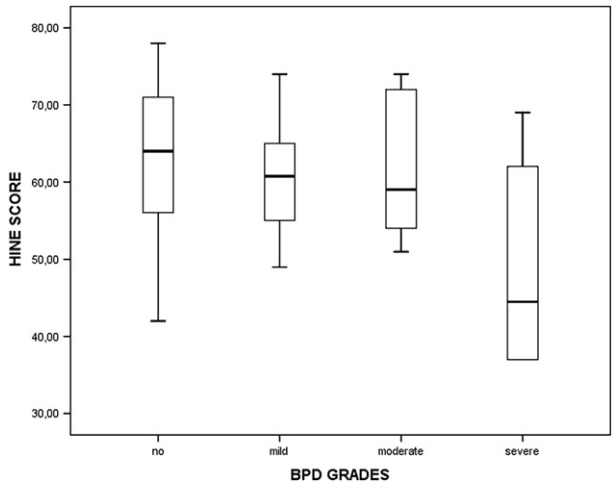

Figure 1. Correlation of bronchopulmonary dysplasia (BPD) grades with scores on Hammersmith Infant Neurological Examination (HINE) at 6 months of corrected age.

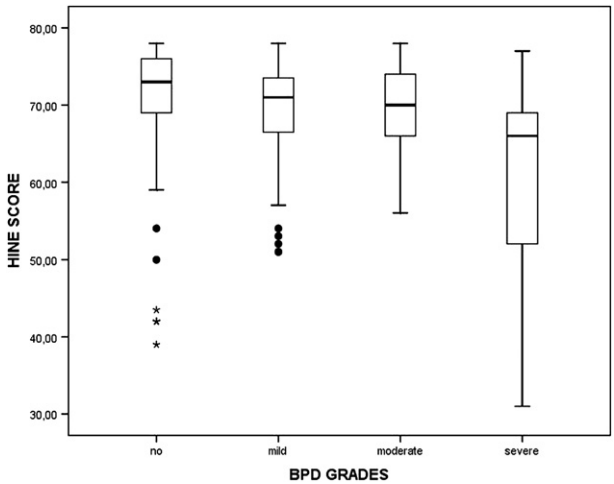

Figure 2. Correlation of bronchopulmonary dysplasia (BPD) grades with scores on Hammersmith Infant Neurological Examination (HINE) at 12 months of corrected age.

Table 3. Neuromotor outcomes at 6 and 12 months of corrected age according to grades of bronchopulmonary dysplasia

	Grades of Bronchopulmonary Dysplasia							
	None	Mild	Moderate	Severe	No vs Mild Bronchopulmonary Dysplasia (*P* Value)	No vs Moderate Bronchopulmonary Dysplasia (*P* Value)	Mild vs Moderate Bronchopulmonary Dysplasia (*P* Value)	Severe vs No, Mild, and Moderate Bronchopulmonary Dysplasia (*P* Value)
6 months of CA global score*	63.4 (± 8.0)	60.7 (± 6.0)	61.8 (± 9.0)	48.6 (± 12.8)	0.14	0.58	0.75	<0.001
≥73, n (%)	13 (8.3)	1 (0.6)	2 (1.3)	0				
64-72, n (%)	46 (29.4)	10 (6.4)	2 (1.3)	2 (1.3)				
37-63, n (%)	47 (30.1)	19 (12.1)	6 (3.8)	8 (5.1)				
12 months of CA global score*	70.7 (± 8.0)	68.4 (± 7.0)	69.1 (± 7.1)	59.6 (± 13.4)	0.14	0.56	0.83	<0.01
≥73, n (%)	64 (36.6)	11 (6.2)	3 (1.7)	1 (0.5)				
64-72, n (%)	45 (25.5)	17 (9.6)	4 (2.2)	5 (2.8)				
31-63, n (%)	12 (6.8)	7 (3.9)	2 (1.1)	5 (2.8)				

* *t* test was used. Data are presented as mean (± S.D.).

Abbreviation:
CA = Corrected age

weight infants throughout infancy [17]. They reported that the inclusion of many small, preterm infants increased the incidence of bronchopulmonary dysplasia and, despite inconsistencies in the diagnosis of bronchopulmonary dysplasia across clinical services, the rates of clinical morbidity by 12 months of corrected age increased as the severity of bronchopulmonary dysplasia worsened. On the other hand, although many small, preterm infants were included in our study, the incidence of bronchopulmonary dysplasia was still low. This finding raises the possibility of differences in perinatal intensive care strategies, such as the administration of surfactant [24]. In our neonatal intensive care unit, infants at high risk for respiratory distress syndrome are electively intubated within 15 minutes after birth for the administration of surfactant, mechanically ventilated for a brief period of time, and promptly extubated to nasal continuous positive airway pressure or atmospheric pressure (dose, 200 mg/kg; Curosurf, Chiesi Farmaceutici SPA, Parma, Italy). Therefore, the differences in our results may have arisen because participants in previous studies were born before the years in which our participants were born. However, infants with severe bronchopulmonary dysplasia as well as those with no, mild, and moderate bronchopulmonary dysplasia experienced progressive increases in global scores from 6 to 12 months of corrected age, whereas infants with periventricular leukomalacia demonstrated a decline in neurologic scores. Ment et al., in a longitudinal study [25], indicated that children with evidence of cerebral injury demonstrated decreased scores in serial verbal and cognitive testing. This finding is in line with the decreased neurologic scores in serial assessments of infants with cystic periventricular leukomalacia in our study.

Our results support the notion that current testing is unable to demonstrate poor neurologic outcomes during the first year of age in infants with severe bronchopulmonary dysplasia. Several studies documented significant deleterious effects of bronchopulmonary dysplasia on motor outcomes [26-28], with early impairments specifically involving hand-eye coordination and postural balance [26]. The impaired control of sensory motor skills may be linked to damage in both the corticospinal tract and the visual pathways [29]. Disrupted brain development is one explanation for the poorer outcomes in infants with bronchopulmonary dysplasia. They are more likely to grow poorly and to exhibit a smaller head circumference [30-32]. Brain development is extremely active during the third trimester, when these children are fighting for survival. During this period, volumes of cortical gray matter increase fourfold, and volumes of white matter increase fivefold [33]. This developmental phase reflects dendritic and axonal ramification, synaptogenesis, glial proliferation and differentiation, and myelination [12]. Diffuse prenatal insults (e.g., perinatal infection leading to cytokine-mediated inflammatory processes) [34] and prolonged periods of hypoxemia [9] were proposed as possible pathophysiologic mechanisms for presumptive neural lesions such as white matter, thalamic, basal ganglia, hippocampal, and cerebellar injuries [13,15]. According to Thompson et al., a major contributor to altered cerebral development in the preterm infant is the presence of bronchopulmonary dysplasia, which was associated with deficits more uniformly distributed across all cerebral regions [35].

This study identified severe bronchopulmonary dysplasia, periventricular leukomalacia, duration of hospital stay, mechanical ventilation, days of oxygen use, patent ductus arteriosus, gestational age, and birth weight as risk factors for poor neuromotor outcome at 6 and 12 months of corrected age. After controlling for all these factors, bronchopulmonary dysplasia and periventricular leukomalacia still exerted a significantly negative effect on

neuromotor outcomes at 6 months of corrected age. At 12 months of corrected age, periventricular leukomalacia and duration of hospital stay were the only factors adversely related to outcomes. Although gestational age and birth weight were significantly higher in the group without bronchopulmonary dysplasia, no significant correlations were evident between these variables and scores on the Hammersmith Infant Neurological Examination at 6 and 12 months of corrected age.

Cystic periventricular leukomalacia was associated with low scores of the the Hammersmith Infant Neurological Examination at 6 and 12 months of corrected age. Several studies documented an association of hemorrhages and periventricular densities with both normal and abnormal neurodevelopment [36-40]. The present study revealed that cystic periventricular leukomalacia adversely affected neuromotor outcomes, and this finding is consistent with those in a recently published study [41]. Cranial ultrasonography was the neuroimaging study of choice, because it is useful in the detection of intraventricular hemorrhage and cystic periventricular leukomalacia, but it demonstrates poor sensitivity in the detection of diffuse white matter abnormalities [42-44].

At our department, intervention services are introduced very early (from 40 weeks of corrected age to 3 months of corrected age), and this policy may account for the better neurologic scores with increasing age in all groups. Maybe infants with white matter injuries related to bronchopulmonary dysplasia achieve higher scores through physiotherapeutic intervention.

Several studies documented that the length of stay in neonatal intensive care exposes very low birth weight infants to a number of uncertain consequences [45]. Evidence has accumulated that the use of bright lights [46,47] may interfere with development, whereas continuous exposure to reduced light affords no benefit [48]. The lack of day-night light cycling [49], excessive noise [50], and increased exposure to nosocomial infections may exert an adverse effect on developmental outcomes.

Our cohort of very low birthweight infants was prospectively enrolled and studied longitudinally from ages 6-12 months. Detailed information was obtained on the prenatal, perinatal, and neonatal course of each child. In addition, the percentage of infants lost to follow-up was clinically similar to the percentage of those who completed the study. Thus, loss to follow-up was unlikely to have influenced the analyses of outcomes.

Our study contains limitations. It did not involve a population-based cohort, which may limit the generalizability of findings to other populations. It did reflect care at a regional neonatal intensive care unit in Greece. On the other hand, only term ultrasonograms were recorded, although serial cranial ultrasonography was performed in each infant. Our findings of significant increases over time in motor outcome are a reflection of the outcome measures used. Different measures could lead to different findings.

Although substantial research has explored the relationship between bronchopulmonary dysplasia and later development, few studies have used a severity-based definition or investigated neurodevelopmental outcomes in preterm infants with bronchopulmonary dysplasia before age 1 year. Studies of interventions designed to prevent the disease should focus on neurodevelopmental outcomes with the most impact on the health of premature infants. Multidisciplinary cooperation by healthcare professionals is needed to plan close follow-up and early intervention programs.

We conclude that bronchopulmonary dysplasia constitutes a major cause for poor neuromotor outcomes at age 6 months, but improvements in motor outcomes occur over time.

References

[1] **Lemons** JA, Bauer CR, Oh W, et al. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 through December 1996. Pediatrics 2001; 107:1-8.

[2] **Bancalari** E, del Moral T. Bronchopulmonary dysplasia and surfactant. Biol Neonate 2001;80(Suppl. 1):7-13.

[3] **Jobe** AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163:1723-9.

[4] **Clark** RH, Gerstmann DR, Jobe AH, Moffitt ST. Lung injury in neonates: Causes, strategies for prevention, and long-term consequences. J Pediatr 2001;139:478-86.

[5] **Eber** E, Zach MS. Long term sequelae of bronchopulmonary dysplasia (chronic lung disease of infancy). Thorax 2001;56:317-23.

[6] **Anderson** PJ, Doyle LW. Neurodevelopmental outcome of bronchopulmonary dysplasia. Semin Perinatol 2006;30:227-32.

[7] **Hack** M, Fanaroff AA. Outcomes of children of extremely low birthweight and gestational age in the 1990s. Semin Neonatol 2000;5:89-106.

[8] **Skidmore** MD, Rivers A, Hack M. Increased risk of cerebral palsy among very low-birthweight infants with chronic lung disease. Dev Med Child Neurol 1990;32:325-32.

[9] **Garg** M, Kurzner SI, Bautista DB, Keens TG. Clinically unsuspected hypoxia during sleep and feeding in infants with bronchopulmonary dysplasia. Pediatrics 1988;81:635-42.

[10] **Singer** L, Martin RJ, Hawkins SW, Benson-Szekely LJ, Yamashita TS, Carlo WA. Oxygen desaturation complicates feeding in infants with bronchopulmonary dysplasia after discharge. Pediatrics 1992;90:380-4.

[11] **Sekar** KC, Duke JC. Sleep apnea and hypoxemia in recently weaned premature infants with and without bronchopulmonary dysplasia. Pediatr Pulmonol 1991;10:112-6.

[12] **Volpe** J. Neurology of the newborn. 4th ed. Philadelphia: W.B. Saunders, 2001. 331-93.

[13] **Fuller** PW, Guthrie RD, Alvord EC. A proposed neuropathological basis for learning disabilities in children born prematurely. Dev Med Child Neurol 1983;25:214-31.

[14] **Als** H, Lawhon G, Duffy FH, McAnulty GB, Gibes-Grossman R, Blickman JG. Individualized developmental care for the very low-birthweight preterm infant. Medical and neurofunctional effects. JAMA 1994;272:853-8.

[15] **Perlman** JM, Volpe JJ. Movement disorder of premature infants with severe bronchopulmonary dysplasia: A new syndrome. Pediatrics 1989;84:215-8.

[16] **Byrne** PJ, Piper MC, Darrah J. Motor development at term of very low birthweight infants with bronchopulmonary dysplasia. J Perinatol 1989;19:301-6.

[17] **Jeng** SF, Hsu CH, Tsao PN, et al. Bronchopulmonary dysplasia predicts adverse developmental and clinical outcomes in very-low-birthweight infants. Dev Med Child Neurol 2008;50:51-7.

[18] **Katz-Salamon** M, Gerner EM, Jonsson B, Lagercrantz H. Early motor and mental development in very preterm infants with chronic lung disease. Arch Dis Child Fetal Neonatal Ed 2000;83:F1-6.

[19] **Northway** WH Jr, Moss RB, Carlisle KB, et al. Late pulmonary sequelae of bronchopulmonary dysplasia. N Engl J Med 1990;323:1793-9.

[20] **Alexander** RG, Kogan DM, Himes HJ. 1994-1996 U.S., singleton birth weight percentiles for gestational age by race, Hispanic origin, and gender. Matern Child Health J 1999;4:225-31.

[21] **Haataja** L, Mercuri E, Regev R, et al. Optimality score for the neurologic examination of the infant at 12 and 18 months of age. J Pediatr 1999;135:153-61.

[22] **Dubowitz** LM, Dubowitz V, Mercuri E. The neurological assessment of the preterm and full-term newborn infant. Clinics in developmental medicine. No. 148. Adaptation of the neurological proforma. 2nd ed. London: MacKeith Press, 1999:147-51.

[23] **Haataja** L, Cowan F, Mercuri E, Bassi L, Guzzetta A, Dubowitz L. Application of a scorable neurologic examination in healthy term infants aged 3 to 8 months. J Pediatr 2003;143:546.

[24] **Soll** R, McQueen MC. Respiratory distress syndrome. In: Sinclair J, Bracken MB, editors. Effective care of the newborn infant. London: Oxford University Press, 1992:325-58.

[25] **Ment** LR, Vohr B, Allan W, et al. Change in cognitive function over time in very low-birth-weight infants. JAMA 2003;289:705-11.

[26] **Katz-Salamon** M, Gerner EM, Jonsson B, Lagercrantz H. Early motor and mental development in very preterm infants with chronic lung disease. Arch Dis Child Fetal Neonatal Ed 2000;83:F1-6.

[27] **Gregoire** MC, Lefebvre F, Glorieux J. Health and developmental outcomes at 18 months in very preterm infants with bronchopulmonary dysplasia. Pediatrics 1998;101:856-60.

[28] **Schmidt** B, Asztalos EV, Roberts RS, Sauve RS, Whitfield MF; for the Trial of Indomethacin Prophylaxis in Preterms Investigators. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birthweight infants at 18 months: Results from the Trial of Indomethacin Prophylaxis in Preterms. JAMA 2003;289:1124-9.

[29] **Skranes** JS, Vik T, Nilsen G, Smevik O, Andersson HW, Brubakk AM. Cerebral magnetic resonance imaging and mental and motor function of very low birth weight children at six years of age. Neuropediatrics 1997;28:149-54.

[30] **Chiriboga** CA, Kuban KC, Durkin M, et al. Factors associated with microcephaly at school age in a very-low-birthweight population. Dev Med Child Neurol 2003;45:796-801.

[31] **O'Shea** TM, Goldstein DJ, deRegnier RA, Sheaffer CI, Roberts DD, Dillard RG. Outcome at 4 to 5 years of age in children recovered from neonatal chronic lung disease. Dev Med Child Neurol 1996;38:830-9.

[32] **Vohr** BR, Coll CG, Lobato D, Yunis KA, O'Dea C, Oh W. Neurodevelopmental and medical status of low-birthweight survivors of bronchopulmonary dysplasia at 10 to 12 years of age. Dev Med Child Neurol 1991;33:690-7.

[33] **Huppi** PS, Warfield S, Kikinis R, et al. Quantitative magnetic resonance imaging of brain development in premature and mature newborns. Ann Neurol 1998;43:224-35.

[34] **Dammann** O, Leviton A. Maternal intrauterine infection, cytokines, and brain damage in the preterm newborn. Pediatr Res 1997;42:1-8.

[35] **Thompson** DK, Warfield SK, Carlin JB, et al. Perinatal risk factors altering regional brain structure in the preterm infant. Brain 2007;130:667-77.

[36] **Pinto-Martin** JA, Riolo S, Cnaan A, Holzman C, Susser MW, Paneth N. Cranial ultrasound prediction of disabling and nondisabling cerebral palsy at age two in a low birth weight population. Pediatrics 1995;95:249-54.

[37] **Piecuch** RE, Leonard CH, Cooper BA, Kilpatrick SJ, Schlueter MA, Sola A. Outcome of infants born at 24-26 weeks' gestation: II. Neurodevelopmental outcome. Obstet Gynecol 1997;90:809-14.

[38] **de Vries** LS, Regev R, Pennock JM, Wigglesworth JS, Dubowitz LM. Ultrasound evolution and later outcome of infants with periventricular densities. Early Hum Dev 1988;16:225-33.

[39] **Dubowitz** LM, Dubowitz V, Palmer PG, Miller G, Fawer CL, Levene MI. Correlation of neurologic assessment in the preterm newborn infant with outcome at 1 year. J Pediatr 1984;105:452-6.

[40] **Catto-Smith** AG, Yu VY, Bajuk B, Orgill AA, Astbury J. Effect of neonatal periventricular haemorrhage on neurodevelopmental outcome. Arch Dis Child 1995;60:8-11.

[41] **Pinto-Martin** JA, Whitaker AH, Feldman JF, Van Rossem R, Paneth N. Relation of cranial ultrasound abnormalities in low birth weight infants to motor or cognitive performance at ages 2, 6 and 9 years. Dev Med Child Neurol 1999;41:826-33.

[42] **Ment** LR, Bada HS, Barnes PD, et al. Practice parameter: Neuroimaging of the neonate: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2002;58:1726-38.

[43] **Maalouf** EF, Duggan PJ, Counsell SJ, Rutherford MA, Cowan F, Azzopardi D. Comparison of findings on cranial ultrasound and magnetic resonance imaging in preterm infants. Pediatrics 2001;107:719-27.

[44] **Inder** TE, Anderson NJ, Spencer C, Wells S, Volpe JJ. White matter injury in the premature infant: A comparison between serial cranial sonographic and MR findings at term. AJNR 2003;24:805-9.

[45] **Merritt** TA, Pillers D, Prows SL. Early NICU discharge of very low birth weight infants: A critical review and analysis. Semin Neonatol 2003;8:95-115.

[46] **Glass** P, Avery GB, Subramanian K, Keys MP, Sostek AM, Friendly DS. Effect of bright light in the hospital nursery on the incidence of retinopathy of prematurity. N Engl J Med 1985;95:313-7.

[47] **Graven** SN, Bowen FW Jr, Brooten D, et al. The high-risk infant environment, part I: The role of the neonatal intensive care unit in the outcome of high-risk infants. J Perinatol 1992;12:164-72.

[48] **Kennedy** KA, Fielder AR, Hardy RJ, Tung B, Gordon DC, Reynolds JD. Reduced lighting does not improve medical outcomes in very low birth weight infants. J Pediatr 2001;139:527-31.

[49] **Committee on Injury and Poison Prevention**, Committee on Fetus and Newborn. Safe transport of premature infants. Pediatrics 1991;87:120-2.

[50] **Zohr** LK, Detraversay J. Premature infant responses to noise reduction by earmuffs: Effects on behavioral and physiologic measures. J Perinatol 1995;15:448-55.