Prediction of Late Death or Disability at Age 5 Years Using a Count of 3 Neonatal Morbidities in Very Low Birth Weight Infants

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Objective To evaluate bronchopulmonary dysplasia (BPD), serious brain injury, and severe retinopathy of prematurity (ROP) as predictors of poor long-term outcome in very low birth weight infants.

Study design We examined the associations between counts of the 3 morbidities and long-term outcomes in 1514 of 1791 (85%) infants with birth weights of 500-1250 g who were enrolled in the Caffeine for Apnea of Prematurity trial from October 1999, to October 2004, had complete morbidity data, and were alive at 36 weeks postmenstrual age (PMA). BPD was defined as use of supplemental oxygen at 36 weeks PMA. Serious brain injury on cranial ultrasound included grade 3 and 4 hemorrhage, cystic periventricular leucomalacia, porencephalic cysts, or ventriculomegaly of any cause. Poor long-term outcome was death after 36 weeks PMA or survival to 5 years with 1 or more of the following disabilities: motor impairment, cognitive impairment, behavior problems, poor general health, deafness, and blindness.

Results BPD, serious brain injury, and severe ROP occurred in 43%, 13%, and 6% of the infants, respectively. Each of the 3 morbidities was similarly and independently correlated with poor 5-year outcome. Rates of death or disability (95% CI) in children with none, any 1, any 2, and all 3 morbidities were 11.2% (9.0%-13.7%), 22.9% (19.6%-26.5%), 43.9% (35.5%-52.6%), and 61.5% (40.6%-79.8%), respectively.

Conclusions In very low birth weight infants who survive to 36 weeks PMA, a count of BPD, serious brain injury, and severe ROP predicts the risk of a late death or survival with disability at 5 years. *(J Pediatr 2015;167:982-6)*.

Immature and very low birth weight infants have a higher risk of childhood disability than fullterm infants.[1] Adverse long-term outcomes such as motor and cognitive impairments or neurosensory deficits are increased in children with bronchopulmonary dysplasia (BPD),[2,3] severe peri- and intraventricular hemorrhages and other types of brain injury,[4,5] systemic infection,[6,7] necrotizing enterocolitis,[8] and severe retinopathy of prematurity (ROP).[9,10]

We have previously shown in 910 extremely low birth weight infants who participated in the Trial of Indomethacin Prophylaxis in Preterms and survived to a postmenstrual age (PMA) of 36 weeks, that a count of BPD, brain injury, and severe ROP was a strong predictor of a late death or survival with impairment at 18 months.[11] This observation was subsequently confirmed in at least 1 other cohort.[12] Although neonatal infection and necrotizing enterocolitis increased the risk of a late death or survival with neurosensory impairment, infection and necrotizing enterocolitis were weaker predictors of poor outcome than BPD, brain injury, and severe ROP and thus were not added to the morbidity count.[13]

For the current study, we evaluated the count of BPD, brain injury, and severe ROP as a predictor of a late death or disability at 5 years in children who participated in the Caffeine for Apnea of Prematurity (CAP) trial.[14] Confirmation of the validity of this simple predictive tool in a new cohort as a predictor of preschool outcomes would justify its use in clinical practice, for example, to target especially high-risk infants for early intervention and long-term follow up.

Methods

Infants with birth weights of 500 to 1250 g were enrolled in the international CAP trial between 1999 and 2004 and followed to a corrected age of 5 years.[14-16] The research ethics boards of all participating clinical centers approved the initial trial protocol and the additional 5-year follow-up. Written informed consent was

BPD	Bronchopulmonary dysplasia
CAP	Caffeine for Apnea of Prematurity
PMA	Postmenstrual age
ROP	Retinopathy of prematurity

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obtained from a parent or guardian of each infant prior to enrollment and again before the assessments at 5 years. Only infants who survived to 36 weeks PMA were eligible for the current study because infants who die early during their stay in the neonatal intensive care unit cannot develop BPD and severe ROP.

Neonatal Morbidities

BPD, brain injury, and severe ROP were pre-specified secondary outcomes in the CAP trial, and all data were collected prospectively in a standardized fashion. BPD was defined by the need for supplemental oxygen at 36 weeks PMA. Cranial ultrasonography to detect brain injury was recommended between days 14 and 28 of life and between 34 and 36 weeks PMA if the infant was still in the study center at that time. The following lesions were considered to indicate the presence of brain injury at any time throughout the neonatal course: intraparenchymal echodense lesions (grade 4 hemorrhage), cystic periventricular leucomalacia, porencephalic cysts, and ventriculomegaly with or without intraventricular hemorrhage (including grade 3 hemorrhage). Severe ROP was defined as unilateral or bilateral disease of stage 4 or 5, or receipt of retinal therapy in at least 1 eye. Infants were screened for ROP according to local nursery protocols.

Outcomes at a Corrected Age of 5 Years

The main outcome at 5 years was a composite of death before a corrected age of 5 years or survival with 1 or more of the following: motor impairment, cognitive impairment, behavior problems, poor general health, severe hearing loss, and bilateral blindness.[14] Motor impairment in the current study was defined as level 2 through 5 using the Gross Motor Function Classification System.[17] Severe cognitive impairment was defined as a full scale IQ of less than 70 (2 SD below the mean of 100) on the Wechsler Preschool and Primary Scale of Intelligence III.[18] Site investigators used their respective national test norms. The full scale IQ was assumed to be less than 70 if the child could not complete the testing because of severe developmental delay or severe autism. A behavior problem was defined as a total problem T score (range 28-100) greater than 69 (2 SD above the mean of 50) on the Parent Form of the Child Behavior checklist.[19] Poor general health included 1 or more of the following: need for supplemental oxygen, positive airway pressure, feeding through a tube or intravenously, seizures occurring more frequently than once per month, or a recent admission to an intensive care unit for complications resulting from a neonatal morbidity. Severe hearing loss was defined as the prescription of hearing aids or cochlear implants, and bilateral blindness as a corrected visual acuity less than 20/200 in the better eye.

Statistical Analyses

All 5-year outcomes in this analysis were dichotomous, and prevalence rates have been presented as percentages with exact 95% CI. Relationships between individual neonatal morbidities and 5-year outcomes were expressed as OR with associated 95% CI based on the approximate SE for log OR. The Fisher exact test was used to assess the significance of an observed OR against the null hypothesis of no relationship (true OR = 1). Various logistic regression models were used to investigate the combined effect of the individual morbidities, the potential lack of additivity, and the gradient of outcome risk with morbidity count. Model-based estimates of OR were derived from the maximum likelihood regression coefficients and the corresponding 95% CI from the SE of these estimates.

Results

A total of 2006 infants with birth weights of 500-1250 g were enrolled in the original CAP trial. Four of 35 clinical centers did not participate in the 5-year follow-up. The remaining 31 centers had enrolled 1932 infants, of whom 1853 survived to 36 weeks PMA. All 3 neonatal morbidities—BPD, brain injury, and severe ROP—were known for 1791 CAP trial participants, of whom 1514 children had adequate data for the analysis of the composite outcome of death or disability at 5 years. The characteristics of the children and their families in this cohort were very similar to the characteristics reported previously for CAP trial participants at 5 years.[14] Mean birth weight (SD) was 962 (180) g and mean gestational age (SD) 27.4 (1.8) weeks.

Univariate Relationships between Neonatal Morbidities and Poor Outcome at 5 Years

Of the 1514 study infants, 657 (43%) children had BPD, 196 (13%) had serious brain injury, and 93 (6.1%) had severe ROP. Each of these 3 neonatal morbidities was strongly associated with a late death after 36 weeks PMA or disability at 5 years. The OR ranged from 2.7 for BPD to 4.0 for severe ROP, with fairly narrow 95% CI (Table I). A logistic model was applied to the data that included a separate indicator variable for each morbidity to allow for inter-correlation between the 3 morbidities. The estimated independent prognostic contribution (labeled as the "Model estimated" OR in Table I) was similar for each of the 3 morbidities. An additional model that included interaction terms suggested that the 3 morbidities provided independent prognostic information, with little evidence of "non-additivity" ($P = .97$).

Combinations of Neonatal Morbidities and Poor Outcome at 5 Years

Table II gives the rates of death or disability at 5 years in infants with all possible combinations of the 3 neonatal morbidities, beginning with infants who survived without BPD, serious brain injury, or severe ROP, and ending with the group of 26 infants who developed all 3 morbidities. The observed rate of death or disability was 11.2% in children who remained free of BPD, brain injury, and severe ROP. This increased to 22.9% with any 1 of the