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Predicting neurosensory disabilities at two years of age in a national cohort of extremely premature infants

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ABSTRACT

Background: Extreme prematurity carries a high risk of neurosensory disability.
Aims: Examine which information obtained pre-, peri- and postnatally may be predictive of neurosensory disabilities at 2 years of age.
Study design: Prospective observational study of all infants born in Norway in 1999 and 2000 with gestational age (GA) 22–27 completed weeks or birth weight (BW) of 500–999 g.
Outcome measures: Incidence of neurosensory disabilities.
Results: Of 373 surviving children, 30 (8%) had major neurosensory disabilities (26 CP, 6 blind, 3 deaf), and a further 46 (12%) had minor visual or hearing disabilities. The rate of major neurosensory disabilities was 19 of 99 (19%) for children with GA 23–25 vs. 8 of 189 (4%) for GA 26–27 weeks ($p<0.001$). In a multivariable model, only morbidities detected in the neonatal intensive care unit (NICU) were associated with major neurosensory disabilities; adjusted odds ratios (95% confidence intervals) were 68.6 (18.7, 252.2) for major abnormalities on cerebral ultrasound, 6.8 (1.7, 27.4) for retinopathy of prematurity (ROP) grade>2, 3.2 (1.0, 9.7) for ROP grade 1–2, 6.5 (1.9, 22.3) for prolonged use (≥21 days) of steroid treatment for lung disease and 3.1 (1.0, 9.4) for clinical chorioamnionitis. The visual outcome was strongly related to the degree of ROP ($p<0.001$), and all who had a normal hearing screen in the NICU had normal hearing at 2 years.
Conclusion: NICU morbidities, rather than GA or intrauterine growth are the significant predictors of major neurosensory disabilities among extreme prematurity surviving to discharge from the NICU.

1. Introduction

During the last decades, survival rates among extremely premature infants have increased due to the use of antenatal steroids and surfactant, as well as advances in medical technology and knowledge [1]. Still, the number of children surviving with disabilities remains high, [2] and may even have increased [3,4]. Therefore, with the advances in care, studies on the outcome are needed in order to identify early clinical characteristics, therapeutic measures and results of diagnostic tests which may be important prognostic factors. In particular, it is important to study the results of providing life support to immature infants at the limit of viability. The lower gestational age (GA) limit for offering life support is a matter of ongoing debate, and recommendations vary from 23 to 26 weeks [5,6].

Neonatologists are challenged with stating prognosis at particularly two stages in the care of premature infants. First, before birth, prediction of survival without substantial sequelae is based on GA,

Abbrevations: GA, Gestational age; SGA, Small for gestational age; BW, Birth weight; NICU, Neonatal Intensive Care Unit; CUS, Cerebral ultrasound; PROM, Prolonged ruptures of membranes; PVH, Periventricular haemorrhage; ROP, Retinopathy of prematurity; PVL, Periventricular leucomalacia; BPD, Bronchopulmonary dysplasia; NEC, Necrotizing enterocolitis; PDA, Persistent ductus arteriosus; CP, Cerebral palsy; OR, Odds ratio; CI, Confidence interval.

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estimated birth weight (BW) and clinical characteristics during pregnancy. We have previously shown that in extremely preterm infants, GA is the dominating predictor of neonatal mortality and morbidity [7]. Next, at discharge from the neonatal intensive care unit (NICU), a developmental prognosis is requested on the basis of the same factors and data obtained from the NICU course. Therefore, accurate evidence based knowledge on the significance of such factors is of paramount importance when deciding on guidelines for management and follow-up, and for advising families. A rational approach to advice on infants born at the threshold of viability is to compare their outcomes with those of infants born less preterm and for whom it is not controversial to offer life support, e.g. infants born at 26 weeks' GA or later.

The aim of the present study was to assess the predictive value of pre-, peri-, and postnatal clinical characteristics and the results of diagnostic examinations performed in the NICU in relation to specific neurosensory disabilities at 2 years of age in children born extremely premature.

2. Patients and methods

2.1. Patients

Data were prospectively collected for all births of infants with GA 22^0 to 27^6 weeks or BW 500 to 999 g born in Norway during 1999 and 2000. Data on outcomes until death or discharged home from the NICU have previously been published [7–10]. Of 638 births, 153 (24%) were stillborn and 21 (3%) died in the delivery room, 15 of them without attempted resuscitation. Outcome was unknown for two infants. Of the remaining 462, 376 (59%) were discharged home alive, i.e. 81% of the admitted babies [7].

2.2. Methods

Data on maternal health, pregnancy, delivery and NICU stay were extracted from the compulsory notification to the Medical Birth Registry of Norway (MBRN) and from registration forms developed for the study [7]. All obstetric and paediatric departments in Norway participated. The extent of routine examinations during the NICU stay was left to the discretion of each unit, but the infants had repeated cerebral ultrasound (CUS) and ophthalmology examinations. The last CUS was performed at or later than 3 weeks of age for 91 of 99 (92%) of those with GA 23–25 weeks, 141 of 189 (75%) with GA 26–27 weeks, and for 64 of 85 (75%) with GA>27 weeks. Before discharge from the NICU, hearing was assessed with brain stem audiometry or otoacoustic emission in most units.

At 2 years, a paediatrician completed forms developed for the study on somatic health and neurological status. They were not blinded to the background of the children.

For children who missed the planned follow-up, data were collected in retrospect from the medical records if a routine follow-up had been performed within 1 year of planned evaluation, and from an additional structured telephone interview (TM).

The study was approved by the Regional Committee on Medical Research Ethics and the Norwegian Data Inspectorate. Parents gave written informed consent.

2.3. Definitions

GA was determined by ultrasound at 17–18 postmenstrual weeks, except for 20 (5%) based on the last menstrual period. Small for gestational age (SGA) was defined as a birth weight<the fifth percentile for post menstrual age, and appropriate for gestational age as birth weight≥the fifth percentile for post menstrual age according to the recently revised sex specific standards for birth weight by post menstrual age in Norway [11]. Prenatal steroids were defined as being given at least 24 h before delivery or at least as two doses. Prolonged rupture of membranes (PROM) was defined as a rupture more than 6 days before delivery, and preeclampsia (including a few cases of HELLP syndrome and eclampsia) as systolic blood pressure (BP)≥140 and/or diastolic BP≥90 in combination with proteinuria. Diagnosis of chorioamnionitis was based on clinical symptoms and findings combined with biochemical and haematological tests. An index of early disease severity, the illness severity score (ISS) was computed from the three components of the clinical risk index for babies, [12] namely the lowest and highest fractional oxygen (FiO_2) requirements and the largest base deficit during the first 12 h of life. Periventricular haemorrhage (PVH) was graded on the basis of cerebral ultrasound (CUS) examinations according to Papile et al., [13] and retinopathy of prematurity (ROP) as defined by the Committee for Classification of Retinopathy of Prematurity [14]. Periventricular leucomalacia (PVL) was graded as either 1–2 small cysts or more extensive lesions (multicystic PVL). Major CUS pathology was defined as PVH grade 3–4 and/or multicystic PVL. Bronchopulmonary dysplasia (BPD) was defined as the need of assisted ventilation or oxygen supplementation at 36 completed postconceptional weeks, [15] and septicaemia as the growth of bacteria or fungi in blood cultures in conjunction with clinical symptoms and supplementary tests consistent with systemic infection [8, 9]. Necrotizing enterocolitis (NEC) included suspected NEC, which was treated accordingly, and proven NEC (pneumatosis and/or perforation). Persistent ductus arteriosus (PDA) included both untreated and treated PDA. Postnatal steroids were dexamethasone given for treatment of lung disease. When missing values counted for less than 2%, and unless otherwise likely, complications were recorded as not being present.

At 2 years' corrected age, major neurosensory disability was defined as cerebral palsy (CP), blindness, meaning that the child was classified as legally blind, or complete deafness. Minor neurosensory disability was defined as one-sided blindness, strabismus, myopia or other visual deficits requiring glasses diagnosed by an ophthalmologist, or decreased hearing.

2.4. Statistical analysis

Independency between categorical variables was tested with the chi-square test or Fisher's exact test, while trends were analyzed with linear-by-linear exact tests. Groups were compared with two-sample Mann–Whitney test or the chi-square test as appropriate. Logistic regression was applied to analyze the risk of neurosensory disability at 2 years' corrected age, according to prenatal and NICU factors. Unadjusted and backward stepwise selection analyses were performed using $p<0.05$ as the inclusion criterion in the likelihood ratio-test (LR-test). Results were expressed as odds ratios (OR) and 95% confidence intervals (CI).

P-values<0.05 were considered significant. Means with standard deviations (SD) or medians with interquartile ranges (IQR) were given as appropriate. SPSS statistical package version 15.0 was used for the analyses.

3. Results

Of the 376 infants discharged from the NICU, three died. Two infants without major morbidity in the NICU died of sudden infant death syndrome, and one from a congenital syndrome. Of the 373 survivors, 343 (92%) met for the follow-up examination at a mean (SD) corrected age of 24 (3) months. For the remaining 30 (8%) children, data were derived from routine medical follow-up records and telephone interviews.

Background data of the survivors are given in Table 1. For the infants treated with postnatal steroids<21 days, the mean (SD) age of starting treatment was 22 (15) days and duration of treatment was 9 (5) days. For those treated≥21 days, treatment was started at day 14