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Neonatal Risk Factors for Treatment-Demanding Retinopathy of Prematurity

A Danish National Study

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Purpose: One goal of the study was to identify "new" statistically independent risk factors for treatment-demanding retinopathy of prematurity (ROP). Another goal was to evaluate whether any new risk factors could explain the increase in the incidence of treatment-demanding ROP over time in Denmark.

Design: A retrospective, register-based cohort study.

Participants: The study included premature infants (n = 6490) born in Denmark from 1997 to 2008.

Methods: The study sample and the 31 candidate risk factors were identified in 3 national registers. Data were linked through a unique civil registration number. Each of the 31 candidate risk factors were evaluated in univariate analyses, while adjusted for known risk factors (i.e., gestational age [GA] at delivery, small for gestational age [SGA], multiple births, and male sex). Significant outcomes were analyzed thereafter in a backward selection multiple logistic regression model.

Main Outcome Measures: Treatment-demanding ROP and its associations to candidate risk factors.

Results: Mechanical ventilation (odds ratio [OR], 2.84; 95% confidence interval [CI], 1.99−4.08; $P < 0.01$) and blood transfusion (OR, 1.97; 95% CI, 1.20−3.14; $P = 0.01$) were the only new statistically independent risk factors, in addition to GA at delivery, SGA, multiple births, and male sex. Modification in these prognostic factors for ROP did not cause an increase in treatment-demanding ROP.

Conclusions: In a large study population, blood transfusion and mechanical ventilation were the only new statistically independent risk factors to predict the development of treatment-demanding ROP. Modification in the neonatal treatment with mechanical ventilation or blood transfusion did not cause the observed increase in the incidence of preterm infants with treatment-demanding ROP during a recent birth period (2003−2008). *Ophthalmology 2016;■:1−8 © 2016 by the American Academy of Ophthalmology.*

Retinopathy of prematurity (ROP) is a proliferative disorder that develops in infants born prematurely. In the 1940s, the disease was first described by Terry.[1] Immaturity was the obvious cause of disease development at that time. Later, other authors found that an excessive amount of oxygen supplementation also induced the disease.[2−4] Over the years, a more restrictive use of oxygen supplements was implemented in the neonatal intensive care units; however, the disease still occurs.[5,6] Several authors suggest that ROP is a multifactorial disease and that additional factors are involved in the pathogenesis.[7−11]

Many studies have described an association between ROP and different prenatal and postnatal factors or neonatal therapies. Thus, a long list of candidate risk factors exists, such as intrauterine growth retardation, multiple births, male sex, nonblack race, postnatal growth retardation, birth in another study center, hypoxemia, hypocabnia/hypercabnia, mechanical ventilation, respiratory distress syndrome, apnea, blood transfusions, sepsis, intraventricular hemorrhage, prolonged parenteral nutrition, methylxanthine administration, treatment with indomethacin, and Norrie disease mutation.[7−36] In many of these studies, only univariate analyses were performed, and confounding variables were not adjusted for.[12−16,18,19,27,32,35,37] The studies in which multivariate analysis was undertaken were all based on small to moderate sample sizes, and the conclusions reached often were controversial.[7−11,17,20,26,28,29,32−34]

This is a national, retrospective, register-based study. On the basis of the current largest study population (n = 6490), the goal of this study was to reduce the current number of potential risk factors for ROP and to identify the statistically independent risk factors for ROP development. Identification of these risk factors allows more stable prediction of high-risk infants. With this knowledge, a more advanced risk-based screening model can be developed.[38] Another goal of this study was to evaluate whether any previously unidentified risk factors could explain a recent increase in the incidence of infants treated for ROP (1% to 4%) in Denmark.[7]

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Methods

This retrospective register-based cohort study includes premature infants born in Denmark from 1997 to 2008. The infants and potential risk factors were identified in 3 national registers. The National Register of Rigshospitalet (NRR) holds information on all the infants with treated ROP in Denmark. The National Birth Registry (NBR) of the National Board of Health (NBH) contains birth-related information. The National Patient Register (NPR) of the NBH holds information on any contact a patient will have with the Danish health care system. It further contains data on admissions to a hospital department, diagnosis and treatments given, and examinations and surgery performed during admission. Data from the different registers were linked through a unique Danish Civil Registration Number.

Identification of Treated Infants

In Denmark, only a few experienced pediatric ophthalmologists perform screening for ROP. They all adhere to the International Classification of Retinopathy of Prematurity revisited.[39] All ROP in need of treatment is centralized to the Eye Department at Rigshospitalet. A small group of ROP experts decide whether ROP treatment should be given. The infants who received ROP treatment were identified in the NRR. Combinations of the ROP International Classification of Diseases, 10th Revision (ICD-10) code, codes for laser/cryotherapy treatment, and codes for vitrectomy and scleral buckling surgery were used. Infants were included in the study sample if they were born during the study period (1997−2008) and treated for ROP. Throughout the study period, the indication for treatment was the presence of threshold ROP, as defined in the Cryotherapy for Retinopathy of Prematurity Cooperative Group study.[40]

Identification of the Cohort of Premature Infants

In Denmark, it is demanded by law that physicians and midwives report birth-related information on all live births to the NBR. Live-born premature infants from the study period were identified in the register, and data were obtained for each included infant. Information on gestational age (GA) at delivery, birth weight (BW), sex, multiple births, and, when relevant, date of death were obtained. In Denmark, ROP screening is performed on all infants born with a GA of less than 32 weeks; only a few more mature infants are also examined if they are very sick. A inclusion criterion of GA <32 weeks was used to identify the cohort of premature infants. This criterion resulted in 6625 infants who were alive at the fifth postnatal week. For each of the infants, a standard deviation (SD) score of BW for GA was calculated.[41] Infants with extreme values of BW were excluded, because the values were most likely typing errors. The values were defined as BW less than +3 SD or BW <−6 SD of the expected from the GA. The final study population comprised 6490 infants.

Data from the National Patient Register

The NPR contains ICD-10 codes for diagnoses and treatment, surgeries that are given to the register at discharge from a hospital, or when there is a transfer from one hospital to another or from one department to another. The ICD-10 codes of potential risk factors for ROP that were given before the 44th postconceptual week were included. The registration of treatment/surgery was not considered accurate before year 2000, and registrations before the year 2000 were excluded from the study.

The relevant disease diagnoses were cerebral hemorrhage, neonatal convulsions, respiratory distress syndrome, bronchopulmonary dysplasia, congenital pneumonia, neonatal pneumothorax, necrotizing enterocolitis, cerebral disorders, meningitis, jaundice of the newborn, anoxia, anoxia during birth, apnea, neonatal anemia, carbohydrate level disturbance, infant of diabetic mother, amnionitis, ductus arteriosus persistence, and congenital sepsis. The treatment and surgery codes were mechanical ventilation, blood transfusion, oxygen treatment, continuous positive airway pressure treatment, surfactant therapy, cardiac stimulant treatment, dopamine treatment, parenteral nutrition (partial/total) and nutrition complication, born by caesarean section, ligation of ductus arteriosus persistence, and surgery for necrotizing enterocolitis. Some physiologic conditions, such as Apgar score, head and abdominal circumference, and placenta weight, were extracted from the birth register. Small for gestational age (SGA) was defined by as BW <2 SD of the expected value for the GA using a fetal growth reference.[41]

Ethics

This study was approved by the Danish Data Protection Agency.

Data Analyses

A total of 31 candidate risk factors for ROP were analyzed one at a time in logistic regression models while adjusted for the known risk factors: GA, SGA, male sex, and multiple births. Candidate risk factors associated with a significantly increased risk were included in a multivariate logistic regression model, which also contained the known risk factors listed earlier. Finally, a stepwise backward elimination was performed to identify the independent risk factors. The study period was divided into 4 subperiods. The birth period of 2000 to 2002 was set as reference to the subperiods. An analysis for period variation was done using 2 separate multiple logistic regression models. Both models were adjusted for known risk factors, the latter also for newly identified risk factors. P values <0.05 were considered statistically significant. All analyses were performed with R version 2.15.3.[42]

Results

Descriptive Data

Figure 1 shows the preterm study population from the birth period 1997 to 2008 (grey dots; 6490 infants). Those infants who received ROP treatment also are marked (black dots; 192 infants). Of note, the occurrence of ROP treatment increases with increasing immaturity. In fact, 19.54% (77/394) of the infants born at a GA of 23 to 25 weeks were treated for ROP. The corresponding numbers for the subgroups of infants born at 26 to 27 weeks, 28 to 29 weeks, and 30 to 31 weeks are 5.81% (58/999), 2.21% (40/1805), and 0.51% (17/3292), respectively. The demarcation line separates the study population into the infants who are SGA (darker grey below the line) and infants who are average for GA/large for GA (lighter grey above the line).

Table 1 presents known risk factors and cases of ROP treatment for 4 subperiods and the entire study period. Except for an increase in infants with treated ROP occurring from 2003 and onward, no major changes were observed over the entire birth period. The incidence of treatment-demanding ROP increased from 1% to 4% during the time period.