Cerebral Damage May Be the Primary Risk Factor for Visual Impairment in Preschool Children Born Extremely Premature

Carina Slidsborg, MD; Regitze Bangsgaard, MD; Hans Callø Fledelius, MD; Hanne Jensen, MD; Gorm Greisen, MD; Morten la Cour, MD

Objectives: To investigate the importance of cerebral damage and retinopathy of prematurity (ROP) for visual impairment in preschool children born extremely premature and to determine the primary risk factor of the two.

Methods: A clinical follow-up study of a Danish national cohort of children born extremely premature (gestational age, <28 weeks). The study sample consisted of 262 extremely preterm children born between February 13, 2004, and March 23, 2006, of whom 178 children (67.9%) participated. A matched control group consisted of 56 term-born children (gestational age, 37 to <42 weeks). All participants were identified through the National Birth Register and invited to participate in a clinical examination. The children were evaluated regarding visual acuity, foveal sequelae, and maximum ROP stage and the presence of global developmental deficits (an indicator for cerebral damage) that was measured by the Ages and Stages Questionnaire.

Results: Global developmental deficits and foveal sequelae occurred more often in extremely preterm children than in term-born control children and increased with ROP severity ($\chi^2$ test; $P=.11$ and $P<.001$, respectively). Global developmental deficits, moderate to severe foveal abnormality, and ROP treatment were independently associated with visual impairment ($P<.05$, for better and worse eyes). A stepwise multiple logistic regression for better-eye logarithmic visual acuities of 0.3 or greater (Snellen scale, ≤0.5) yielded an odds ratio of 8.7 (95% CI, 3.0-25.2; $P<.001$) for global developmental deficit and 6.3 (95% CI, 2.2-18.5; $P<.001$) for moderate to severe foveal sequelae.

Conclusion: Cerebral damage and ROP are independent risk factors for visual impairment in children born extremely premature, and cerebral damage may be the primary risk factor.


Retinopathy of Prematurity (ROP) is considered the main cause of visual impairment in extremely preterm children (gestational age [GA], <28 weeks). However, since the implementation of ROP screening programs and retinal ablative treatment regimens and the improvement of neonatal care, some highly developed countries have experienced a reduction in childhood blindness due to ROP.

Cerebral damage is another cause of visual impairment (termed cerebral visual impairment) in extremely preterm children. In daily clinical ophthalmologic practice, cerebral damage is not considered a contributor to visual impairment until it is established that ocular pathologic findings (mainly foveal sequelae) cannot account for the entire extent of visual impairment. Thus, cases of coexisting cerebral damage may remain undiagnosed, leaving pediatric ophthalmologists with the impression that ROP is still the primary risk factor for visual impairment in extremely preterm children. Recent international studies express increasing incidences of cortical damage in childhood blindness. However, the relative importance of cortical damage and ROP for visual impairment among children born preterm is unclear.

In cases of cerebral damage, cortical developmental disturbance resulting from preterm birth per se and cerebral lesions (eg, intraventricular hemorrhage, hydrocephalus, and periventricular leukomalacia) during the neonatal period should be considered. Both cortical developmental disturbance and cerebral lesions may be followed by cascades of generalized destructive processes in the maturing brain that will eventually result in wide-ranging cerebral destruction in childhood. Neurodevelopmental (or neuropsychological) tests may...
therefore be more reliable than historical markers to detect the presence of cerebral damage and cerebral visual impairment in extremely preterm children. In this study, we used a valid and reliable developmental test, the Ages and Stages Questionnaire (ASQ); an abnormal test score indicated global developmental deficits.

This clinical follow-up study included a national cohort of preschool children born extremely premature and a matched term-born sample born in Denmark between February 13, 2004, and March 23, 2006 (corrected age for the extremely preterm children), and were approximately 4 years of age on the examination day.

From the NBR, 476 extremely preterm children born before 28 weeks' GA were identified. Obvious registration errors, such as less than 20 weeks' GA or birth weight larger than twice the expected birth weight for their GA, resulted in exclusion of 32 children (6.7%). Another 182 children (38.2%) were excluded because they died before the search date. Of the 262 remaining extremely preterm children, 42 (16.0%) were unreachable because of faulty contact information or "indisposition to research." Another 4 children (1.5%) were excluded because the parent was incapable of completing a Danish written developmental questionnaire. Finally, parents of 38 children (14.5%) were not interested in participating. Most nonparticipating children were seen regularly by a pediatric ophthalmologist and, according to their parents, had good VA. A total of 178 of the 262 available children (67.9%) participated in the examination.

Of the term-born cohort (GA, 37 to <42 weeks), a random sample of 87 term-born children was selected that matched (1:1) residential postal codes of a random sample of extremely preterm children, 42 (16.0%) were unreachable because of faulty contact information or "indisposition to research." Another 4 children (1.5%) were excluded because the parent was incapable of completing a Danish written developmental questionnaire. Finally, parents of 38 children (14.5%) were not interested in participating. Most nonparticipating children were seen regularly by a pediatric ophthalmologist and, according to their parents, had good VA. A total of 178 of the 262 available children (67.9%) participated in the examination.

EXAMINATION PROCEDURES

Before the eye examination day, the ASQ was completed by the parents, partly from memory and partly through exercises with the children. The ASQ is a valid and reliable way to assess development. It investigates 5 developmental areas, namely, communication, gross and fine motor skills, problem solving, and personal and social skills. Each section includes 6 questions, and each question is scored as zero (not yet), 5 (sometimes), or 10 (yes). Thus, the possible total ASQ raw score for a given child ranges from 0 to 300 and represents the child's general developmental ability.

The presence of global developmental deficits was defined as an ASQ standard deviation score (SDS) less than −2. A linear regression was fitted to the total ASQ raw scores (ASQ) of the term-born children and their postconceptional age (PCA) on evaluation. The following equation was used to calculate the expected total ASQ raw score (ASQe):

$$\text{ASQe} = -41.135 + 0.146 \times \text{PCA},$$

in which PCA is expressed in days. The ASQ SDS could then be calculated as follows:

$$\text{ASQ SDS} = \frac{(\text{ASQ} - \text{ASQe})}{\text{SD}_{\text{ASQ}}},$$

in which SD_{ASQ} is the standard deviation calculated from the individual total ASQ raw score for the term-born sample.

The children were included for examination according to their PCA, starting with the oldest ones first. Most of the children (65.7%) were examined during their fourth birth year (corrected age for extremely preterm children). No age difference was found between the study groups (Kruskal-Wallis test, P = .07).

A fundus camera (TRC-NW-6S; Topcon Medical Systems, Inc) was used to obtain 45 color fundus photographs centered on the macula. The grading of the photographs was performed by a single experienced pediatric ophthalmologist (H.C.F.), who was masked to the birth and disease status of the children until after the grading was performed. The fundus photographic scoring system consisted of the Iovea scores (Fs), for which 0 indicates normal; 1, a lack of foveal reflex; 2, foveal heterotopia or retinal pigment epithelial scarring; 3, foveal folds; and 4, retinal retinoschisis or detachment involving the fovea. Because only 2 children had an F5 greater than 2 (in the worse eyes), the remaining Fs categories (Fs ≥ 2) were gathered into a single category, hereinafter referred to as "moderate to severe F5." An F5 of 1 was considered "mild F5." The pathologic features (except lack of foveal reflex) were defined earlier, and the reliability of the fundus photographic scoring system was confirmed. Several international studies subsequently have applied similar or analogous systems.

The luminance for visual testing was standardized between 50 and 120 candles/m² using an exposure meter (Scout 3; Gosen Foto und Lichtmetstechnik GmbH) according to the ETROP (Early Treatment for ROP) protocol. The cohort underwent best-corrected distance VA measurement using the linear letter logMAR HOTV chart, a valid and reliable method. All VAs are given in logarithmic (Snellen scale) VAs. The visual testing was performed by a single experienced pediatric ophthalmologist (R.B.), who was masked to the birth and disease status of the children until after the testing was performed. One child with monocular light perception was given a logMAR scale VA of 2 (Snellen scale, 0.01). After visual testing, the pupils were dilated with cyclopentolate hydrochloride, 1%. Refraction was performed by use of an automatic refractor/keratometer (Retinomax K-plus 3; MMC Optical AVS). Eventual refractive errors were corrected and the VA retested according to the ETROP protocol.

SELECTION BIAS

To evaluate selection bias in the study sample, the immaturity of the participating and nonparticipating children as well as other characteristics, such as sex, small for GA, and multiple birth, along with diagnosis revealing presence of ROP or brain-
related abnormalities, were acquired from the NBR and the National Patient Registry. In addition, a search of the National Registry of Blind and Visually Impaired Children (NRBVIC) revealed whether the nonparticipating visually impaired or blind children were primarily registered because of brain-related abnormalities or ROP sequelae. In Denmark, registration in the NRBVIC of children who have a logMAR VA of 0.52 or greater (Snellen scale, ≤0.3) in the better eye when initially examined is mandatory by law. The data retrieved from these 3 registries (NBR, National Patient Registry, and NRBVIC) are linked unambiguously through a unique individual civil registration number provided at birth by the National Board of Health.

**STUDY GROUPS**

All ophthalmologic departments involved in the screening for ROP were contacted to retrospectively retrieve information on the premature infant’s maximum acute ROP stage. Five study subgroups of extremely preterm children were defined: all extremely preterm (n = 178), extremely preterm without ROP (n = 99), extremely preterm with regression of acute ROP (n = 47), extremely preterm with any stage of acute ROP (n = 79), and extremely preterm receiving treatment for ROP (n = 32). (The extremely preterm subgroups will be referred to in this sequence; the preterm subgroups are not mutually exclusive.) A control group consisted of term-born children (n = 56).

**STATISTICAL ANALYSIS**

All data sets were investigated for normality to determine whether parametric or nonparametric methods should be used. Nonparametric analysis of variance on ranks (the Kruskal-Wallis test) was used for comparison of continuous variables involving 3 or more groups. The Dunn test was used to correct for multiple comparisons when testing individual subgroups. The χ² test was used to compare categorical variables. Post-hoc correction was performed by use of the Bonferroni adjustment. The significance level of the estimated variables of the multiple logistic regression analysis was assessed using the Wald statistic. Throughout the analysis, we used a confidence interval of 95% and a significance level of P < .05. Statistical analysis was performed using Sigma Stat software (SigmaStat Software).

**RESULTS**

The proportion of children with global developmental deficits increased from 2 of 56 children (3.6%) in the term-born control group to 21 of 178 (11.8%), 7 of 99 (7.1%), 8 of 47 (17.0%), 14 of 79 (17.7%), and 6 of 32 (18.8%) in the all extremely preterm, extremely preterm without ROP, extremely preterm with regression of acute ROP, extremely preterm with any stage of acute ROP, and extremely preterm receiving treatment for ROP groups, respectively. The occurrence of global developmental deficits (ASQ SDS < −2) tended to increase with increasing ROP severity (Figure 1). However, the occurrence of global developmental deficits did not differ significantly between the 6 subgroups (χ² test; P = .11).

For the better-eye VAs, the proportion of children given a score of abnormal fovea (FS ≥ 0) was 6 children (10.7%) in the term-born control group and increased through the 5 extremely preterm subgroups (28 children [15.7%], 1 [1.0%], 8 [17.0%], 27 [34.2%], and 19 [59.4%]) (Figure 2). For the better-eye VAs, the proportion of mild foveal sequelae (FS = 1) and moderate-to-severe FS (FS ≥ 2) differed significantly between the subgroups (χ² test; P = .02 and P < .001, respectively).

For the worse-eye VAs, the proportions of children with an abnormal fovea were 6 children (10.7%) for the term-born control group and 42 children (23.6%), 13 (13.1%), 6 (12.8%), 29 (36.7%), and 23 (71.9%) for the 5 extremely preterm subgroups (Figure 2). For the worse-
eye VAs, the proportions were significantly different for moderate to severe FS ($\chi^2$ test; $P < .001$).

The subgroup of extremely preterm children receiving treatment for ROP had significantly more mild FS than did the term-born control group and the extremely preterm children without ROP ($\chi^2$ test; $P = .01$ and $P = .002$, respectively, for the better-eye VAs). Similar results were reached for the proportion of moderate to severe FS ($\chi^2$ test; $P < .001$ for both the better- and worse-eye VAs).

**VISUAL OUTCOME DATA**

For better- and worse-eye VAs, the difference between the 3 ASQ SDS subgroups was statistically significant (Kruskal-Wallis test; $P < .001$ for both). However, after multiple comparisons correction, only the global developmental deficit subgroup remained significantly different (Dunn test; $P < .05$ for both) (Figure 3). Among the children with global developmental deficits, 10 of 21 children (47.6%) and 14 (66.7%) had a logMAR VA of 0.3 or greater (Snellen scale, $\leq 0.5$) for the better- and worse-eye VAs, respectively.

For better- and worse-eye VAs, the 3 FS subgroups were significantly different (Kruskal-Wallis test; $P < .001$ for both VAs). However, after correction for multiple comparisons, only eyes having moderate to severe FS showed significantly reduced VAs compared with eyes with no FS (Dunn test; $P < .05$ for better- and worse-eye VAs) (Figure 4).

Among the children who had moderate to severe FS, 10 of 23 children (43.5%) and 14 of 24 (58.3%) had a logMAR VA of 0.3 or greater (Snellen scale, $\leq 0.5$) for the better- and worse-eye VAs, respectively. The VAs decreased with increasing severity of ROP sequelae (Table 1), and the 6 study groups were significantly different (Kruskal-Wallis test; $P < .001$ for better- and worse-eye VAs). After correction for multiple comparisons, the VAs of the extremely preterm children receiving treatment for ROP remained significantly lower compared with the term-born control group and the extremely preterm children without ROP (Dunn test; $P < .05$ for better- and worse-eye VAs). Furthermore, a significant reduction in VAs was also seen for all extremely preterm children and extremely preterm

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**Figure 2.** Proportions of different maximum fovea scores (FSs) for the 6 study subgroups for eyes of better (A) and worse (B) visual acuities. ROP indicates retinopathy of prematurity.

**Figure 3.** The association between developmental level and better-eye (A) or worse-eye (B) visual acuities (VAs). The data are presented in 3 columns according to the children’s developmental ability: high normal (ie, Ages and Stages Questionnaire [ASQ] standard deviation score [SDS] above the mean), low normal (ie, ASQ SDS from 0 to $–2$ SDS below the mean), and global developmental deficit (ASQ SDS $< −2$ SDS below the mean). The data are presented as median logarithmic VAs (horizontal line inside the box), with upper and lower quartiles (box limits), maximum and minimum values (whiskers), and a few outliers (solid circles). After exclusion of children recorded with any abnormal foveal sequelae, the data remained largely the same.
children with regression of acute ROP compared with the term-born control group (Dunn test; P < .05 for better- and worse-eye VAs). Finally, the extremely preterm children without ROP had significantly reduced VAs compared with the term-born control group (Dunn test; P < .05 for the better-eye VAs). In fact, for the better-eye VAs, 9 of the 178 extremely preterm children (5.1%) compared with 1 of the 56 term-born children (1.8%) had abnormal VAs (logMAR VA ≥0.3 [Snellen scale, ≤0.5]) when first examined that could not be explained by cerebral damage or ROP sequelae.

**MULTIPLE LOGISTIC REGRESSION ANALYSIS**

Several stepwise logistic regression analyses were performed to reveal the primary risk factor for visual impairment (logMAR VA, ≥0.3 [Snellen scale, ≤0.5]). The discriminative analysis used global developmental deficits (ASQ SDS ≤2), moderate to severe FS (FS ≥2), and ROP treatment as independent variables (**Table 2**). For each analysis, a reduced discriminative model resulted in 2 significant variables: global developmental deficit and advanced retinal disease (moderate to severe FS or a history of ROP treatment). For better- and worse-eye VAs, 28 of the 178 extremely preterm children (15.7%) and 48 (27.0%) were attributed logMAR VAs of 0.3 or less (Snellen scale, ≤0.5). The reduced models with an outcome variable of logMAR VA of 0.3 or greater (Snellen scale, ≤0.5) resulted in odds ratios of 8.7 (95% CI, 3.0-25.2; P < .001) for global developmental deficit and 6.3 (2.2-18.5; P < .001) for moderate to severe FS for the better-eye VAs and 7.3 (2.6-20.8; P < .001) for global developmental deficits and 6.5 (2.7-15.5; P = .003) for the presence of ROP treatment for the worse-eye VAs.

This is the first study, to our knowledge, to evaluate on the basis of clinical variables the relative importance of cerebral damage and ROP sequelae as risk factors for visual impairment in extremely preterm children. For many years, ROP has been considered the main cause of visual impairment in extremely preterm children. However, this study demonstrates that cerebral damage is the primary risk factor for visual impairment (logMAR VA, ≥0.3 [Snellen scale, ≤0.5]). Furthermore, in visually impaired children (logMAR VA, ≤0.3 [Snellen scale, ≤0.5]), 4 of 12 children (33.3%) with foveal abnormalities (FS ≥2) also have cerebral damage when first examined. This raises concerns that, in the current clinical ophthalmologic setting, ROP sequelae are given too much importance and cerebral damage is given too little importance when attributing the cause of visual impairment.

The clinical implications for these results should be that pediatric ophthalmologists and pediatricians look beyond ROP and consider cerebral damage in all premature infants, even in cases in which blindness or visual impairment may be explained by the current ROP sequelae. Detection of cerebral damage and cerebral visual impairment in extremely preterm children allows referral to multidisciplinary teams specializing in clinical assessment and rehabilitation. In the clinical ophthalmologic setting, cerebral damage in a child could be detected by administration of the ASQ. This method is valid, reliable, inexpensive, and easy to implement.

**COMMENT**

Despite a moderate participation rate of 67.9%, concerns were raised about selection bias, which could affect the validity of the conclusions. To explore this matter further, the incidence of children with developmental deficits or ROP sequelae was calculated. In our study sample, the incidence of developmentally impaired children was low (11.8%) compared with other international studies (7%-30%). However, the incidence of moderate (10.1% vs 3.9%) and severe (0.6% vs 0.4%-0.7%) foveal sequelae in our cohort tended to be high compared with other recent international studies. These incidences suggest that the study sample could be slightly biased. To investigate the occurrence of selection bias, 2 additional investigations were performed. First, a search in the National Patient Registry for diagnoses relevant to a reduced visual out-

**Table 1. Better- and Worse-Eye Logarithmic Visual Acuities Among the 6 Study Groups**

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Better Eye</th>
<th>Worse Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term-born children</td>
<td>0.09 (0.06)</td>
<td>0.12 (0.06)</td>
</tr>
<tr>
<td>Range</td>
<td>0.00 to 0.03</td>
<td>0.00 to 0.30</td>
</tr>
<tr>
<td>All extremely preterm children</td>
<td>0.17 (0.15)</td>
<td>0.24 (0.23)</td>
</tr>
<tr>
<td>Range</td>
<td>−0.10 to 0.95</td>
<td>0.00 to 2.00</td>
</tr>
<tr>
<td>Extremely preterm children without ROP</td>
<td>0.14 (0.11)</td>
<td>0.17 (0.11)</td>
</tr>
<tr>
<td>Range</td>
<td>−0.10 to 0.62</td>
<td>0.00 to 0.62</td>
</tr>
<tr>
<td>Extremely preterm children with regression of acute ROP</td>
<td>0.18 (0.17)</td>
<td>0.25 (0.22)</td>
</tr>
<tr>
<td>Range</td>
<td>−0.10 to 0.81</td>
<td>0.00 to 1.28</td>
</tr>
<tr>
<td>Extremely preterm children with any stage of acute ROP</td>
<td>0.20 (0.18)</td>
<td>0.31 (0.30)</td>
</tr>
<tr>
<td>Range</td>
<td>0.10 to 0.95</td>
<td>0.00 to 2.00</td>
</tr>
<tr>
<td>Extremely preterm children receiving treatment for ROP</td>
<td>0.24 (0.18)</td>
<td>0.40 (0.38)</td>
</tr>
<tr>
<td>Range</td>
<td>0.00 to 0.95</td>
<td>0.00 to 2.00</td>
</tr>
</tbody>
</table>

**Figure 4.** The association of no, mild, and moderate to severe fovea score (FS) and better-eye (A) or worse-eye (B) visual acuities (VAs). Graph elements are explained in the legend to Figure 3. After exclusion of children having a global developmental deficit, the VAs improved moderately in all subgroups.

**Abbreviation:** ROP, retinopathy of prematurity.
come among the entire study cohort showed that more nonparticipants were registered with a neurological diagnosis (eg, epilepsy \( P = 0.01 \), hearing loss \( P = 0.06 \), and hydrocephalus \( P = 0.07 \); Table 3) compared with study participants. No major differences were found between participants and nonparticipants for the occurrence of ROP. Second, a search in the NRBVIC demonstrated that more of the nonparticipating extremely preterm children (7 of 9 cases \( 77.8\% \)) were registered because of neurological damage rather than for ROP sequelae (9 of 178 children \( 5.1\% \)). Both investigations suggested that selection bias could have resulted in an underestimation of cerebral damage and an overestimation of ROP as the causes of visual impairment in preschool children born extremely premature. However, the conclusions reached after the discriminative analysis would not be affected by this finding.\( ^{35} \)

In our study, a higher proportion of extremely preterm children compared with term-born children had abnormal VAs (logMAR VA, \( \geq 0.3 \) [Snellen scale, \( \geq 0.5 \]) when first examined that could not be explained by cerebral damage or ROP sequelae (9 of 178 children [5.1\%] vs 1 of 56 [1.8\%] for the better eyes). Other international reports\( ^{7,10,36,37} \) have suggested that this increase in the occurrence of usually subtle visual impairment among extremely preterm children may be the result of preterm birth per se, neonatal environmental factors, or even insensitivity of the fundus photographic scoring system to detect minor retinal abnormalities. Only a few term-born children in our study were scored as having ROP sequelae (all except one were scored as having mild foveal sequelae); thus, the fundus photographic scoring system we applied appears valid for the purpose of our study. Future studies are urgently needed to clarify the underlying causes for visual impairment in extremely preterm children with no apparent abnormalities.

This study should be seen in light of some potential limitations. First, only a trend of association was detected between global developmental deficits and maximum acute ROP stage. Another report\( ^{38} \) found a stronger association. The developmental questionnaire we used is a valid and reliable test\( ^{19-23} \); therefore, a lack of test suitability is an unlikely cause. We believe that erroneous baseline data (ie, inaccurate registration of the maximum acute ROP stage in the hospital records) and the small sample size are more likely explanations.

Second, it is important to unravel the exact extent to which visual impairment per se could have influenced the level of developmental deficits in the extremely preterm children studied. A recent study\( ^{39} \) suggested that only severe visual impairment (logMAR VA, \( \geq 1.0 \) [Snellen scale, \( \geq 0.1 \)]) in both eyes affects functional deficits. Because no such cases were found in our study, the conclusions reached after the discriminative analysis are not considered to be influenced by visual impairment per se.

### Table 2. Discriminative Analyses for LogMAR VA of 0.3 or Greater (Snellen Scale, \( \geq 0.5 \))

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Better-Eye VA, OR (95% CI)</th>
<th>P Value</th>
<th>Worse-Eye VA, OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>0.1 (0.0-0.1)</td>
<td>&lt;.001</td>
<td>0.2 (0.1-0.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ASQ SDS ( \leq -2 )</td>
<td>8.1 (2.8-23.5)</td>
<td>&lt;.001</td>
<td>7.1 (2.5-20.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>FS ( \geq 2 )</td>
<td>4.7 (1.5-14.7)</td>
<td>.007</td>
<td>2.2 (0.7-6.3)</td>
<td>.16</td>
</tr>
<tr>
<td>ROP treatment</td>
<td>2.2 (0.8-6.4)</td>
<td>.14</td>
<td>5.1 (2.0-13.0)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: ASQ, Ages and Stages Questionnaire; FS, fovea score; OR, odds ratio; ROP, retinopathy of prematurity; SDS, standard deviation score; VA, visual acuity.

### Table 3. Birth, Neurological, and Retinal Characteristics of the Participating and Nonparticipating Extremely Preterm Children

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Participants (n=178)</th>
<th>Nonparticipants (n=84)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, mean (SD) [range], d</td>
<td>186 (7.3 [163-195])</td>
<td>186 (7.8 [152-195])</td>
<td>.83</td>
</tr>
<tr>
<td>Birth weight, mean (SD) [range], g</td>
<td>900 (200) [458-1843]</td>
<td>914 (203) [600-1730]</td>
<td>.56</td>
</tr>
<tr>
<td>Male sex</td>
<td>94/178 (53.8)</td>
<td>43/83 (51.8)</td>
<td>.86</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>32/178 (18.2)</td>
<td>14/83 (16.9)</td>
<td>.96</td>
</tr>
<tr>
<td>Multiple births</td>
<td>69/176 (39.2)</td>
<td>30/83 (36.1)</td>
<td>.85</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
<td>65/178 (36.5)</td>
<td>29/83 (34.9)</td>
<td>.98</td>
</tr>
<tr>
<td>Received treatment</td>
<td>33/178 (18.5)</td>
<td>16/83 (19.3)</td>
<td>.97</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>36/178 (20.2)</td>
<td>17/83 (20.5)</td>
<td>.90</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>3/178 (1.7)</td>
<td>6/83 (7.2)</td>
<td>.07b</td>
</tr>
<tr>
<td>Periventricular leukomalacia</td>
<td>7/178 (3.9)</td>
<td>3/83 (3.6)</td>
<td>.82</td>
</tr>
<tr>
<td>Meningitis</td>
<td>0/178</td>
<td>2/83 (2.4)</td>
<td>.20</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>0/178</td>
<td>3/83 (3.6)</td>
<td>.08b</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>5/178 (2.8)</td>
<td>10/83 (12.0)</td>
<td>.01b</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>0/178</td>
<td>2/83 (2.4)</td>
<td>.20</td>
</tr>
</tbody>
</table>

\[ a \] The numbers of positive and total cases available in the National Birth Register and National Patient Registry are given because the denominator varied.

\[ b \] Indicates a significant or borderline-significant P value.
Third, 5 of the extremely preterm children were amblyopic. Consequently, some worse-eye VAs were underestimated. However, these few cases will not influence the conclusions reached after the discriminative analysis.

Finally, this study was conducted on retrospective registry data. Although the registry data are considered complete and highly accurate, the conclusions should be confirmed by other retrospective or, preferably, prospective studies. Countries with less-developed health services typically have a higher incidence of retinal disease and consequently may show a different risk profile for visual outcome.

In conclusion, we herein demonstrate that, in Denmark, cerebral damage and ROP sequelae are independent risk factors for VA loss (ie, logMAR VA, ≥0.3 [Snellen scale, ≤0.5]) among preschool children born extremely premature and that the presence of cerebral damage may be the primary risk factor of the two. Ophthalmologists should be alert to whether cerebral damage (and, consequently, cerebral visual impairment) is present in children born extremely premature. This will ensure that relevant measures are taken to refer children with cerebral damage to a multidisciplinary team specializing in the clinical evaluation and rehabilitation of children with cerebral visual impairment.

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Correspondence: Carina Slidsborg, MD, Department of Ophthalmology, Glostrup Hospital, Nordre Ringvej 57, 2600 Glostrup, Denmark (carinaslidsborg@hotmail.com).

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