Neurodevelopmental Outcomes among preterm infants surviving Necrotizing Enterocolitis Compared to Matched Controls: A 5-Year Follow-up Study

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Abstract

Aim: To compare neurodevelopmental outcomes between preterm infants surviving necrotizing enterocolitis (NEC) and preterm infants without NEC at 5 years of age.

Methods: This was a retrospective matched-control study of preterm infants born between 1996 and 2006. The cohort included preterm infants (gestation ≤32 weeks and/or birth weight <1.500 grams) surviving NEC, who were followed up at 5 years of age (n = 58). The children were matched with two preterm children without NEC (n = 110), when available. Our outcome measures were growth data, the Movement Assessment Battery for Children (M-ABC), the Revised Amsterdam Child Intelligence Test (RAKIT), a child behavior checklist (CBCL), and a teacher report form (TRF).

Results: The perinatal characteristics did not differ, except that there were more preterm infants surviving NEC who were small for their gestational ages (62.7% versus 40.0%; p = 0.001). There was no significant difference in mean outcome of M-ABC, RAKIT, CBCL and TRF between children surviving NEC and children without NEC.

Conclusion: Mean neurodevelopmental outcome seems not to differ between preterm infants surviving NEC and preterm infants without NEC at 5 years of age when matching on age and maternal education. However, results need to be replicated in a larger study.

Keywords: Necrotizing Enterocolitis, Preterm Infants, Motor performance, Cognition, Maternal Education

Introduction

Necrotizing enterocolitis (NEC) is the most common gastrointestinal emergency among preterm infants, causing significant mortality and morbidity [1]. The cause of NEC is yet unknown, but there are at least twenty reported risk factors that might influence its onset [2]. Researchers have suggested that the combination of genetic predisposition, intestinal immaturity, imbalance in microvascular tone, formula feeding, abnormal bacterial colonization, and a highly active intestinal mucosa can lead to intestinal inflammation [3, 4]. Morbidity and mortality rates (20–40%) are high among infants with NEC, and previous research has shown that preterm infants with NEC might be at risk for developing long-term neurodevelopmental impairment [5]. Research also shows that preterm infants who survive NEC have an increased risk for damage to the grey and white matter in their brains [6, 7].

The number of studies that reported poor neurodevelopmental outcomes analyzing long-term follow-up screening is limited [8-10]. Although some studies have assessed neurodevelopmental outcomes among preterm infants surviving NEC and preterm infants without NEC, none of these studies have taken maternal education into account, even though research shows that this

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Received: June 27, 2019; Accepted: July 03, 2019; Published: July 08, 2019

*This article is reviewed by “Sirin”(USA)
has an important impact on an infant’s neurodevelopmental outcome [11-13]. We hypothesized that matching infants based on maternal education is of high importance and will influence the efficacy of comparing the neurodevelopmental outcomes between preterm infants surviving NEC and preterm infants without NEC. The aim of this study was to compare the growth and neurodevelopmental outcome at 5 years of age, of preterm infants surviving NEC and preterm infants without NEC. Next, we compared surgically treated infants to conservatively treated infants to analyze the long-term outcomes, and taking the severity of NEC into context. And considering maternal education as a point of contextual influence of infant neurodevelopment.

Methods

Participants

This study is a between-group comparison embedded in a retrospective 10-year cohort study, born between 1996 and 2006. The participants were selected from the cohort of preterm infants (gestation ≤ 32 weeks and/or birth weight < 1,500 grams) who had been treated at the neonatal intensive care unit. All children who visited the follow-up outpatient clinic at 5 years of age were eligible. The age-5 follow-up is a standard, multidisciplinary program for preterm infants during which children visit a pediatrician, a pediatric physical therapist, and a pediatric psychologist. The perinatal data for all preterm infants in the cohort were extracted from the National Neonatal Registration (NNR) database.

First, a neonatologist selected preterm infants who suffered from NEC and checked for the correct diagnoses of NEC in their medical files. The diagnosis of NEC was divided into 6 stages according to Bell: 1A, 1B, 2A, 2B, 3A, and 3B [14]. For each preterm infant surviving NEC, two control preterm infants without NEC were selected. Matching was based on maternal education, birth year, gender, and minus or plus two weeks gestation. For the infants with a birth weight of < 1,500 grams but with a gestational age above 32 weeks, we matched them to control infants with a gestational age that was one or two weeks below them. Follow-up information from both groups were then collected. The study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. The local ethics committee reviewed the study and waived the need for approval (number 2018-4631).

Multidisciplinary program

During the age-5 follow-up appointments, a pediatrician performed a general assessment of each child’s health, growth, and development by taking their medical history and performing a physical examination. The pediatric physical therapist assessed motor performance with the Movement Assessment Battery for Children (M-ABC). The follow-up program used the first version of M-ABC until 2003 and then switched to the second version, the M-ABC-II. We used the norm references for Dutch children (both versions have acceptable validity and reliability). Through 2003, to determine a delay in motor performance, we used a cut-off point at or below the 15th percentile. After 2003, the cut-off point we used was at or below the 16th percentile, which conforms to both manuals [15, 16]. In addition, at the follow-up appointments, a psychologist assessed cognition using the short version of the Revised Amsterdam Child Intelligence Test (RAKIT), a reliable, validated, often-referenced Dutch instrument containing 6 subtests. We converted the raw subtest scores into standardized scores, which we then transformed into a short RAIT intelligence quotient (IQ). Cognitive delay was defined by a test result below -1 standard deviation (SD) (i.e., an IQ below 85) [17]. Each child’s mother and/or father completed a child behavior checklist (CBCL), and each child’s teacher filed a teacher report form (TRF). We summed all of these items into a total score and recalculated these scores into percentiles. Scores of 59 or less were classified as “within normal range,” whereas scores above 60 are classified as “delayed” [18].

Statistical Analyses

Descriptive statistics were used to present the characteristics of the children and our chosen outcome measures. We analyzed the differences in baseline characteristics between preterm infants surviving NEC and preterm infants without NEC using a Chi-square or a Fisher’s Exact Test. We compared the perinatal factors (sepsis, peri-intraventricular hemorrhage (PIVH), periventricular, leukomalacia (PVL), post-hemorrhagic ventricular dilatation (PHVD), convulsions, retinopathy of prematurity (ROP), patent ductus arteriosus (PDA), infant respiratory distress syndrome (IRDS)) among preterm infants surviving NEC who attended their age-5 follow-up appointments and those who did not with Chi-Square or Fisher’s Exact Test. Multilevel, linear regression analyses were performed to compare height, weight, head circumference, IQ, CBCL- and TRF-reported behavior, and M-ABC scores between the children surviving NEC and children without NEC. A random intercept model was used with the matching group (one NEC child with two control children) as a randomizing factor. Further, multilevel regression analyses were conducted to compare conservatively treated preterm infants to surgically treated preterm infants with NEC and to compare NEC groups stage 1A and 1B versus stages 2A,2B,3A and 3B. To compare the frequency of abnormal results in the domains of neurodevelopmental outcome, Chi-Square or Fisher’s exact test was used. A two-sided p-value of < 0.05 was considered statistically significant. Data were analyzed with SPSS version 22.

Results

A total of 152 preterm infants (gestation ≤ 32 weeks and/or birth weight ≤ 1,500 grams) diagnosed with NEC were born between 1996 and 2006. Thirty-four children (22.4%) died in the first twenty eight days of their life. Eleven (11.2%) died after 28 days or after discharge. Of the total of 101 children who survived, 58 (57.4%) visited the 5-year follow-up, and thus were eligible for the study. Forty-three infants (42.6%) could not be included in the study because they did not visited...
the 5-year follow-up. The reasons for lost to follow-up were: 8 refused, 9 moved away and 26 were untraceable. The 58 children who were eligible for the study, were matched with 110 peers. Six children with NEC had only one control match (all others had after two), because a second child who met all the criteria was not available in our database.

In total, the data of 168 children were analyzed. The children surviving NEC consisted of 30 boys (51.7%) and 28 girls (48.3%); the children without NEC consisted of 54 boys (49.1%) and 56 girls (50.9%). The mean gestational age for both groups was 29.5 weeks [SD of -1.9]. The mean birth weight did not differ between the groups, but there were statistically more preterm infants surviving NEC who were small for their gestational ages (SGA) (p = 0.001). The median education of the mother was intermediate vocational education; and there was no difference in distribution of maternal education between both groups (p = 0.553).

Table 1 shows no statistically significant difference in the stages of NEC between preterm infants who did or did not attend their age-5 follow-up appointments (n = 58 versus n = 46, respectively; p = 0.708). We compared the perinatal factors of both groups and found no statistical differences in any of the factors. Table 2 describes the perinatal characteristics of preterm infants surviving NEC and preterm infants without NEC. The groups did not differ in perinatal characteristics that could have influenced neurodevelopmental outcomes.

**Growth and neurodevelopmental outcomes among preterm infants surviving NEC and preterm infants without NEC**

Differences in mean weight, height, head circumference, M-ABC-, CBCL-, and TRF-reported behavior scores were not statistically significant between the children surviving NEC and children without NEC. In all, 9 children were not able to perform the RAKIT test, 6 children surviving NEC and 3 without NEC. Reasons for dropout were visually impairment (NEC n = 3), cerebral palsy (NEC n = 1, control n = 1), hemiplegia (NEC n = 1), and refusal to perform the tasks (NEC = 1, control n = 2). Of the remaining children, the difference in IQ scores were not statistically significant (table 3).

**Outcomes between conservatively versus surgically treated preterm infants surviving NEC**

From the 58 preterm infants surviving NEC, 36 infants (62.1%) were conservatively treated for NEC, whereas 22 infants (37.9%) were surgically treated. There were no statistically significant differences between the conservatively treated NEC infants (n = 36) and the surgically treated NEC infants (n = 22) in mean weight, height, head circumference, IQ scores, CBCL- and TRF-reported behavior scores, and M-ABC scores (table 4).

**Neurodevelopment outcomes per NEC stages**

There were no statistically significant differences between preterm infants with stage-1A and -1B NEC (n = 26; 44.8%) and preterm infants with the stage 2A-, 2B-, 3A-, and 3B-NEC (n = 32; 55.2%) in mean weight, height, head circumference, IQ scores, M-ABC, IQ, and CBCL- and TRF-reported behavior scores (table 4).

**Neurodevelopmental outcome classifications**

The distribution of normal and delayed outcomes did not differ in a statistically significant way among children surviving NEC and children without NEC in the following domains:

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Preterm infants with NECa who attended follow up</th>
<th>Preterm infants with NECa lost to follow up</th>
<th>Total (%)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal factors</td>
<td>Preterm infants with NECa who attended follow up</td>
<td>Preterm infants with NECa lost to follow up</td>
<td>Total (%)</td>
<td>p-value*</td>
</tr>
<tr>
<td>Sepsis (NEC who attended n = 57, lost to follow-up n = 43)</td>
<td>38 (38.0)</td>
<td>29 (29.0)</td>
<td>69 (69.0)</td>
<td>0.554</td>
</tr>
<tr>
<td>PIVH</td>
<td>10 (9.9)</td>
<td>5 (5.0)</td>
<td>15 (14.9)</td>
<td>0.543</td>
</tr>
<tr>
<td>PVL</td>
<td>2 (2.0)</td>
<td>3 (3.0)</td>
<td>5 (5.0)</td>
<td>0.36</td>
</tr>
<tr>
<td>PHVD</td>
<td>0 (0.0)</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
<td>0.426</td>
</tr>
<tr>
<td>Convulsions</td>
<td>8 (7.9)</td>
<td>6 (5.9)</td>
<td>14 (13.7)</td>
<td>0.601</td>
</tr>
<tr>
<td>ROPb (NEC who attended n = 57, lost to follow-up n = 41)</td>
<td>9 (9.2)</td>
<td>7 (7.1)</td>
<td>16 (16.3)</td>
<td>0.963</td>
</tr>
<tr>
<td>PDAb</td>
<td>21 (20.8)</td>
<td>10 (9.9)</td>
<td>31 (30.7)</td>
<td>0.212</td>
</tr>
<tr>
<td>IRDSb</td>
<td>31 (30.7)</td>
<td>18 (17.8)</td>
<td>49 (48.5)</td>
<td>0.743</td>
</tr>
<tr>
<td>NEC stages</td>
<td>0.614</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1A and B</td>
<td>26 (25.7)</td>
<td>15 (14.9)</td>
<td>41 (40.6)</td>
<td></td>
</tr>
<tr>
<td>2A and B</td>
<td>12 (11.9)</td>
<td>13 (12.9)</td>
<td>25 (24.8)</td>
<td></td>
</tr>
<tr>
<td>3A</td>
<td>5 (5.0)</td>
<td>5 (5.0)</td>
<td>10 (9.9)</td>
<td></td>
</tr>
<tr>
<td>3B</td>
<td>15 (14.9)</td>
<td>10 (9.9)</td>
<td>25 (24.8)</td>
<td></td>
</tr>
</tbody>
</table>

Numbers for weight, height, and head circumference; ABC-movement score; RAKIT score; and CBCL-reported behavior scores are displayed as means ± (standard deviation).

a NEC = necrotizing enterocolitis, b M-ABC = Assessment Battery for Children raw score, c RAKIT = Revised Amsterdam Child Intelligence Test, d CBCL = child behavior checklist, e TRF = teacher report form.
• Motor skills: (n = 168), Chi-square: 31/27 (53.4/46.6%) versus 71/39 (64.5/35.5%), (p = 0.16)
• Cognitive skills: (n = 159), Chi-square: 44/8 (84.6/15.4%) versus 89/18 (83.2/16.8%), (p = 0.18)
• Behavioral skills: (n = 168), Chi-square: 48/10 (82.8/17.2%) versus 95/15 (86.4/13.6%), (p = 0.53)

Most children surviving NEC or children without NEC (46.6% and 35.5%) scored “delayed” in the motor domain. None of the children surviving NEC scored “delayed” in all domains, but among children without NEC, 4 children scored “delayed” in all domains. The children who were not able to perform the RAKIT test were not taken into account (NEC children, n = 6; 10.3% and controls, n = 3; 2.7%). When comparing the perinatal factors between the NEC children and control children who were not able to perform the RAKIT rest, we found no difference. There was no difference in mean weight, height, head circumference and TRF total score between the NEC children versus control.
children who were not able to perform the RAKIT. But, comparing the MABC score of these children, NEC children scored a mean of 3.3 [SD of 7.44] versus the control children, who scored a mean of 13.36 [SD of 12.1] (p = 0.16). And for the CBCL total, the NEC children scored a mean of 55.33 [SD of 1.2] versus the control children who scored a mean of 55.33 [SD of 1.2] (Figure 1).

**Discussion**

In this 5-year follow-up, mean neurodevelopmental outcome seems not to differ between preterm infants surviving NEC and preterm infants without NEC. These children were matched on birth year, gender, gestational age, and maternal education. We found no differences when comparing NEC stage 1A and 1B versus 2A, 2B, 3A, and 3B, nor did we find differences among conservatively treated NEC infant patients versus surgically treated NEC infant patients. We only found a statistically significant difference in one characteristic, more preterm infants surviving NEC were classified as SGA than infants without NEC were. Our data is in contrast with other reports [1, 8-10, 19-24]. Most literature that reports significant differences in some or all of these areas analyzed children at age two or younger, whereas this study examined the neurodevelopmental outcomes of children at the age of 5 years [1, 19-24]. Analyzing the neurodevelopmental outcome at the age of 5 is important because at the age of 2 or younger, children surviving NEC need to recover from their period of critical illness. Thus, assessing the neurodevelopmental outcomes of these children at age 5 might be more reliable.

Another important difference between our study and previous

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**Table 4:** Outcomes between conservatively versus surgically treated preterm infants and NEC stage 1A+B versus 2A+B & 3A+B.

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Conservative n = 36</th>
<th>Surgical n = 22</th>
<th>Multilevel linear regression</th>
<th>NEC stage 1A+B n = 26</th>
<th>NEC stage 2A+B &amp; 3A+B n = 32</th>
<th>Multilevel linear regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>Mean (SD) 17.3 (2.9)</td>
<td>Mean (SD) 17.9 (3.0)</td>
<td>p-value 0.569</td>
<td>Mean (SD) 17.4 (2.5)</td>
<td>Mean (SD) 17.6 (3.4)</td>
<td>p-value 0.815</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>Mean (SD) 109.0 (4.7)</td>
<td>Mean (SD) 110.1 (4.8)</td>
<td>p-value 0.408</td>
<td>Mean (SD) 109.4 (5.0)</td>
<td>Mean (SD) 109.4 (4.6)</td>
<td>p-value 0.949</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>Mean (SD) 50.4 (1.9)</td>
<td>Mean (SD) 50.4 (1.8)</td>
<td>p-value 0.984</td>
<td>Mean (SD) 50.9 (1.7)</td>
<td>Mean (SD) 50.0 (1.8)</td>
<td>p-value 0.088</td>
</tr>
<tr>
<td>M-ABC&lt;sup&gt;a&lt;/sup&gt; score</td>
<td>Mean (SD) 26.4 (28.9)</td>
<td>Mean (SD) 34.1 (24.8)</td>
<td>p-value 0.306</td>
<td>Mean (SD) 27.6 (31.0)</td>
<td>Mean (SD) 31.0 (25.0)</td>
<td>p-value 0.622</td>
</tr>
<tr>
<td>RAKIT&lt;sup&gt;a&lt;/sup&gt; score</td>
<td>Mean (SD) 96.7 (12.7)</td>
<td>Mean (SD) 99.5 (12.5)</td>
<td>p-value 0.43</td>
<td>Mean (SD) 95.2 (14.3)</td>
<td>Mean (SD) 99.8 (10.7)</td>
<td>p-value 0.188</td>
</tr>
<tr>
<td>CBCL&lt;sup&gt;a&lt;/sup&gt; mother</td>
<td>Internalizing 50.6 (11.4)</td>
<td>Mean (SD) 47.1 (11.5)</td>
<td>p-value 0.254</td>
<td>Mean (SD) 49.9 (11.8)</td>
<td>Mean (SD) 48.8 (11.5)</td>
<td>p-value 0.704</td>
</tr>
<tr>
<td>Externalizing 49.2 (10.7)</td>
<td>Mean (SD) 47.3 (10.7)</td>
<td>p-value 0.551</td>
<td>Mean (SD) 49.7 (11.1)</td>
<td>Mean (SD) 47.5 (10.4)</td>
<td>p-value 0.436</td>
<td></td>
</tr>
<tr>
<td>Total 50.0 (10.9)</td>
<td>Mean (SD) 47.2 (10.9)</td>
<td>p-value 0.352</td>
<td>Mean (SD) 49.9 (11.5)</td>
<td>Mean (SD) 48.1 (10.6)</td>
<td>p-value 0.532</td>
<td></td>
</tr>
<tr>
<td>TRF&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Internalizing 51.3 (10.3)</td>
<td>Mean (SD) 46.1 (9.8)</td>
<td>p-value 0.093</td>
<td>Mean (SD) 49.0 (9.1)</td>
<td>Mean (SD) 50.1 (10.5)</td>
<td>p-value 0.706</td>
</tr>
<tr>
<td>Externalizing 50.9 (7.9)</td>
<td>Mean (SD) 51.5 (7.2)</td>
<td>p-value 0.788</td>
<td>Mean (SD) 52.3 (8.3)</td>
<td>Mean (SD) 50.1 (7.2)</td>
<td>p-value 0.349</td>
<td></td>
</tr>
<tr>
<td>Total 51.6 (9.1)</td>
<td>Mean (SD) 49.0 (8.7)</td>
<td>p-value 0.361</td>
<td>Mean (SD) 51.3 (9.2)</td>
<td>Mean (SD) 50.2 (8.4)</td>
<td>p-value 0.697</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Head circumference: conservative n = 34, surgical n = 20, NEC stage 1A+B n = 25, NEC stage 2A+B & 3A+B n = 29. <sup>b</sup>M-ABC: Assessment Battery for Children raw score. <sup>c</sup>RAKIT: Revised Amsterdam Child Intelligence Test. <sup>d</sup>CBCL: child behavior checklist. <sup>e</sup>TRF: teacher report form.

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**Figure 1:** VENN diagrams of number of children surviving NEC and children without NEC with delay in development of motor, IQ, behavior, and their mutual overlaps.
literature is our use of maternal education as an important factor in matching infants surviving NEC to those without NEC. Maternal education can be an important source of bias because the education levels of parents (especially mothers) can influence neurodevelopmental outcomes of their children [11-13]. We did find a statistical difference when comparing the characteristics of the groups. We found more SGA among the preterm infants surviving NEC, in whom we expected more delayed neurodevelopmental outcomes, but we did not find differences in outcomes between the groups. Previous studies have solely found neurodevelopmental delay among surgically treated NEC infants, but not in those conservatively treated. This is likely related to the severity of NEC [1, 19, 21]. Of the preterm infants in this study, 62.1% were conservatively treated of whom 44.8% had NEC stage 1. This large proportion is probably one of the reasons for our relatively comparable mean outcome among children surviving NEC and children without NEC. Hence, conservatively treated Bell stage 1 NEC presumably have better circulatory states and reduced inflammatory mediators compared to surgically treated or NEC stage 2 and 3 children [14]. However, comparing the outcome of the conservatively treated group with the surgically treated group did not show any statistically significant differences, and when we compared the outcomes between the group with NEC stage 1 and the group with NEC stages 2 and 3, we found no statistically significant differences. Multiple factors might play a role in this, including a discrepancy between the group who came to follow-up appointments and the group lost to follow-up (42.6%). It is uncertain if follow-up dropout rates lead to a lower or higher incidence of impaired neurodevelopmental outcome, although the drops-outs in our study were comparable to the group who came to follow-up for the perinatal risk factors. Therefore, we do not know if the incidence of neurodevelopmental outcomes among preterm infants surviving NEC might be under- or overestimated in the current data [25]. At last, nine children (NEC n=6, control n=3) could not be included in the RAKIT analysis. When comparing the perinatal factors between these children we found no difference. But, comparing the MABC score and CBCL total score of the NEC children versus the control children who where not able to perform the RAKIT test, the NEC children score lower on both tests. Thus, the mean RAKIT score of the NEC children could be an overestimation.

Limitations
No follow-up data about 5-year-old children born after 2006 were available to us, so our retrospective cohort study could only analyze data from children born between 1996 and 2006. Although these data are not recent, they are still relevant for the current situation because the treatment protocol for preterm infants with NEC at NICU has not changed since then. Unfortunately, maternal education information was not available about preterm infants surviving NEC who were lost to follow up.

Conclusion
In this single-center cohort study, it seems that there is no difference in neurodevelopmental outcome among preterm infants surviving NEC and preterm infants without NEC at the 5-year follow-up assessment point when matched on maternal education, birth year, gender, and gestational age. We recommend that future follow-up studies replicate this study in a larger setting.

References

Matrix options
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Pediatr Res Child Health

Volume 2(2): 2019


