Cerebral Palsy and Neonatal Death in Term Singletons Born Small for Gestational Age

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ABBREVIATIONS: CI—confidence interval, CP—cerebral palsy, CPRN—Cerebral Palsy Registry of Norway, IUGR—intrauterine growth restriction, MBRN—Medical Birth Registry of Norway, OR—odds ratio, SGA—small for gestational age

WHAT’S KNOWN ON THIS SUBJECT: Children born small for gestational age (SGA) have increased risk of perinatal morbidity and mortality, neonatal death, and cerebral palsy (CP). Causes of SGA, such as congenital malformations, intrauterine infections, and preeclampsia, are also risk factors for the same outcomes.

WHAT THIS STUDY ADDS: In 90% of singletons born SGA, CP is apparently of prenatal origin. Low proportions of intrapartum events leading to CP could not be fully explained by a higher neonatal mortality rate in SGA than in non-SGA children.

Dr Stoknes performed the statistical analyses, wrote the first version of the paper, and completed the final version; Dr Irøgens was principally responsible for the data from the Medical Birth Registry, and contributed significantly to the design of the study as well as interpretation of the data; Dr Andersen, M. O. Dahlseng, and Drs Skranes and Salvesen contributed significantly to the interpretation of the data: Dr Andersen as pediatrician, M. O. Dahlseng as medical research student, Dr Skranes as neuropediatrician, and Dr Salvesen as obstetrician; and Dr Vik initiated the project and, together with Dr Kurinczuk, supervised the analyses and the interpretation of the data. All authors have contributed significantly to the drafting and critically reviewed the final version of the article.

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Children born small for gestational age (SGA), a proxy for intrauterine growth restriction (IUGR), have excess risk of neonatal death, encephalopathy in the newborn period, and cerebral palsy (CP). Consistent with this, some authors have found that the risk of CP in children born SGA was confined to those born with low Apgar scores. Blair and Stanley suggested that perinatal hypoxia-ischemia probably played a causal role in <2% of CP patients born SGA. In a more recent review, Stanley, Blair, and Alberman proposed several additional possible pathways that would explain the association between IUGR and CP. Thus, antenatal causes could be brain malformations or intrauterine infections leading to IUGR and CP as independent events. Furthermore, the brain injury might be a result of chronic or acute hypoxemia during pregnancy because of poor placental function (commonly seen in early-onset and severe pre-eclampsia), at birth, or even later caused by the IUGR itself. Unraveling causal pathways leading to CP among children born SGA is further complicated by the fact that children with antenatal brain injuries have low Apgar scores at birth. Finally, because CP may be considered an intermediate outcome between normal birth and neonatal death, it may be important to take into consideration the higher risk of neonatal death among children born SGA. To our knowledge, this perspective has not been addressed in previous studies of the events leading to CP in children born SGA. Thus, the higher risk of CP among children born SGA is poorly understood, and studies addressing the mechanisms have shown diverse results, ranging from all cases being attributed to perinatal hypoxia-ischemia, to nearly all being attributed to antenatal events, considering the perinatal hypoxia-ischemia as a result rather than a cause.

In the current study, we have used available data from the Cerebral Palsy Registry of Norway (CPRN) and the Medical Birth Registry of Norway (MBRN) to explore risk factors and probable timing of events leading to CP in infants born SGA allowing for the higher risk of neonatal mortality in these children.

METHODS

Study Design

All Norwegian children born alive at term as singletons between January 1, 1996 and December 31, 2003 were eligible for inclusion. Data were abstracted from the MBRN and the CPRN. The MBRN prospectively records perinatal data on all births in Norway based on compulsory notification. In total, there was an average of 58,700 births per year in the study period. Clinical data on children with CP were provided by the CPRN. CP data were collected between 2003 and 2011, when the children were at least 4 years of age. The linkage of data between the MBRN and the CPRN was enabled by the national identification number allocated to every individual at birth.

Study Population

During the study period 1996–2003, altogether 456,952 children were born alive; 30,147 were born preterm (<37 gestational weeks), and data on gestational age were missing in 18,143. Among children born at term, 400,488 were singletons. Altogether, 1020 children were subsequently diagnosed with CP. Among these, CPRN had information on 342 children born as singletons at term. Thus, the final study population comprised 342 term singletons with CP and 400,146 term singletons without CP (see Figs 1 and 2, Supplemental Information). Of the total population of singletons born at term, 36,604 (9%) were born SGA, and among the 342 children with CP, 69 (20%) were born SGA.

Study Variables

Antenatal variables obtained from the MBRN included maternal age, maternal disease, and complications during pregnancy (Supplemental Table 4). Birth information included gestational age, placental abruption, induction, cesarean delivery, the vital status of the infant (live or stillbirth), Apgar score at 1 and 5 minutes, birth weight, height and head circumference, and any malformations identified at birth. SGA was defined as a birth weight below the 10th percentile, gender- and parity-specific. Neonatal mortality was defined as the death of a live-born child before 28 completed days after birth. CP was diagnosed and classified according to the recommendations by the Surveillance of Cerebral Palsy in Europe. The bilateral spastic subtype was further classified into the quadriplegic, and the diplegic subtype was based on the Swedish (Hagberg) classification of CP subtypes. Other information obtained from the CPRN registry included congenital malformations. Since 1999, the CP registration form has included specific information from descriptions of cerebral MR findings, namely, normal or abnormal. If abnormal, clinicians were asked to indicate pathologic findings in the periventricular white matter, corpus callosum, basal ganglia, or the cerebellum, and if lesions were focal, or diffuse cortical, as well as bilateral, or unilateral. Age (months) at the MRI examination was also recorded. MR data were available for 160 children. Based on the combined data on Apgar score, MRI findings, CP subtype, potential prenatal risk factors including congenital malformations as recorded in both registries, and intrapartum risk factors, 2 of the authors (G.L.A. and J.S.,
both senior neuropediatricians) independently assessed whether the cause of CP in individual cases was more likely to be of an antenatal origin or due to a stressful event during birth (see Criteria for timing of event in Supplemental Information). The agreement between the 2 pediatricians was excellent as assessed by a Cohen $\kappa$ coefficient$^{13}$ of 0.89 (95% confidence interval [CI]: 0.83–0.94). Finally, consensus between the 2 pediatricians was reached on those few cases about which they had disagreed in their independent assessments. In the assessment of the timing of insults leading to neonatal death and overall adverse outcome, we relied on “low” Apgar score, defined as a score $\leq 3$, suggesting an intrapartum event, and “high” Apgar score, defined as a score $>3$. Major congenital malformations were also allowed for in these analyses.

**Statistical Methods**

Statistical analyses of the data were performed by using SPSS version 19 (SPSS Inc, Chicago, IL). Odds ratios (ORs) with CIs were calculated as estimates of the relative risk of CP if low Apgar scores were present, by using children with high Apgar scores as reference group. $\chi^2$ test or Fisher exact test were used as appropriate to compare differences in proportions between groups. CIs (95%) for prevalence estimates were calculated by using the Wilson (score) method, as recommended by Newcombe and Altman.$^{14}$

**Ethics**

Written informed consent to record clinical data on children in the CPRN and linkage to the MBRN was obtained from the parents. The Regional Ethical Committee for medical research in Mid-Norway approved the study, including the use of deidentified data on children without CP abstracted from the MBRN (reference number 2011/754).

**RESULTS**

Among 400 488 singletons born at term, 36 604 (9%) were born SGA, 580 (0.1%) had low Apgar scores, 398 420 (99.5%) had high Apgar scores, while data on Apgar score were missing in 1488 (0.4%) children. Compared with non-SGA newborns, infants born SGA were at higher risk of low Apgar scores (OR: 1.8; CI: 1.4–2.2), and they had an increased odds of CP (OR: 2.6; CI: 2.0–3.4) and of neonatal death (OR: 3.9; CI: 3.1–4.9) (Table 1). There was a more frequent occurrence of a range of

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**FIGURE 1**
Flowchart, children with CP.

**FIGURE 2**
Flowchart, study population.
pregnancy risk factors except for bleeding and premature rupture of membranes >24 hours among SGA compared with non-SGA children (Supplemental Table 4). Among 342 term singletons with CP, 69 (20%) were born SGA (Table 1).

Congenital malformations and maternal disease were the most common antenatal risk factors, occurring in ~10% of children with CP, but the proportion of children with these risk factors did not differ between the SGA and the non-SGA group (Supplemental Table 5). However, among CP children with a probable intrapartum origin, the proportion of children born after placental abruption and induction of labor was higher among SGA than among non-SGA children (Supplemental Table 5). Among the 160 children with CP and MRI findings, 37 children were born SGA, whereas 123 were born non-SGA (Supplemental Table 6). In the SGA group, 15 (41%; CI: 26–57) children had white matter injury suggestive of an ischemic or inflammatory event in midpregnancy versus 36 (29%; CI: 22–38) in the non-SGA group, whereas 3 (8%; CI: 3–21) had congenital malformations versus 14 (11%; CI: 7–18) in the non-SGA group. None of these proportions differed significantly between the 2 groups. Cortical injury was present in 9 (24%; CI: 13–40) of the SGA children and in 31 (25%; CI: 18–34) of the non-SGA children, whereas basal ganglia injury was found in 5 (14%; CI: 6–28) of the SGA children and in 18 (15%; CI: 10–22) of the non-SGA children. Taking into consideration Apgar score, risk factors, and subtype of CP, 1 of 9 cases with cortical injury and 2 of 5 cases with basal ganglia injury were considered to be of intrapartum origin in the SGA group, corresponding to 8% (CI: 3–21) of SGA children with CP and MRI. Likewise, 4 of 31 cases with cortical injury and 7 of 18 cases with basal ganglia injury were considered to be of intrapartum origin in the non-SGA group, corresponding to 18% (CI: 12–26) of non-SGA children with CP and MRI.

The occurrence of CP among children with low Apgar scores was similar for SGA (7%) and non-SGA (6%) children, whereas the proportions that died in the neonatal period, as well as overall adverse outcome (ie, neonatal death and CP), was borderline higher among SGA than among non-SGA newborns (Table 2). However, when children with major congenital malformations at birth were excluded, the occurrence of neonatal death did not differ significantly between SGA and non-SGA children, nor did overall adverse outcome (ie, CP and neonatal death) (Table 2).

Among children with high Apgar scores, overall adverse outcome (neonatal death and CP) was more common among SGA than among non-SGA children, even when newborns with congenital malformations were excluded (Table 2).

Among the 69 children with CP born SGA, an adverse event during birth was considered the most likely origin on expert review of CP in 5 cases, corresponding to 7% (CI: 3–16) of all SGA children with CP (Table 3). In 3 of the 5 cases placental abruption was recorded. The probable cause was considered to be of antenatal origin in 59 cases (86%; CI: 75–92) (Table 3), and 5 cases could not be classified. In the 263 non-SGA children with CP (Table 1), an intrapartum event was assessed as probable in 31 (12%; CI: 8–16) children, not significantly different from the proportion in the SGA group (P = .28) (Table 3).

The analyses described above were also performed with SGA defined as birth weight below the fifth percentile (Supplemental Tables 7 through 9). The results were not different from those presented above.

**DISCUSSION**

We found that probable intrapartum events were not more often involved in the etiology of CP in SGA than in non-SGA infants, and that ~90% of children with CP born SGA probably had an antenatal origin of their CP. Neonatal mortality did not differ between SGA and non-SGA children with low Apgar scores, when congenital malformations were excluded. Moreover, the proportion of children with antenatal risk factors for CP did not differ between SGA and non-SGA infants, whereas among children with a probable intrapartum origin of their CP, we found placental abruption to occur more often among SGA than among non-SGA children. On MRI, a significant proportion of children with CP in both groups had white matter injury.

**TABLE 1** Total Number (n) of Singletons Born Alive at Term, SGA Singletons, and the Number (n) and Proportion (per 1000) of Singletons Who Died in the Neonatal Period or Who Were Diagnosed With CP

<table>
<thead>
<tr>
<th>Group</th>
<th>Live Born, n</th>
<th>Neonatal Death</th>
<th>CP</th>
<th>Neonatal Death, OR (CI)</th>
<th>CP, OR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (per 1000)</td>
<td>n (%)</td>
<td>n (per 1000)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>All children</td>
<td>400 488</td>
<td>401 (1.0)</td>
<td>0.1</td>
<td>342 (0.9)</td>
<td>0.1</td>
</tr>
<tr>
<td>SGA</td>
<td>36 604</td>
<td>104 (2.8)</td>
<td>0.3</td>
<td>89 (1.9)</td>
<td>0.2</td>
</tr>
<tr>
<td>Non-SGA</td>
<td>563 307</td>
<td>285 (0.7)</td>
<td>0.1</td>
<td>265 (0.7)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

The table also shows ORs with 95% CIs for neonatal death and CP among singletons born alive in Norway during 1996–2003.
A strength of this study is the prospective recording of clinical data in the MBRN and that the diagnosis of CP was made in accordance with European guidelines when the children were at least 4 years of age.\(^1\) By restricting the analyses to singletons born at term, confounding by preterm and/or multiple births was excluded.\(^{15,16}\) Therapeutic hypothermia was not used in Norway until 2007 and can therefore not have had any impact on our results.\(^{17}\) Another limitation is that we had to use proxies for intrapartum stress, including Apgar score <4, or an expert assessment based upon the combination of low Apgar score and other available data. Clinical information, for instance, the presence of neonatal encephalopathy and/or seizures, was missing. We also did not have information on intrauterine exposure to infection. Moreover, it is not uncomplicated to use MRIs to determine the timing of brain injuries. Sie et al\(^18\) suggested that MRI findings depend more on the type of injury than the age at occurrence. However, there was excellent agreement in the independent assessment of the timing of the injuries between the 2 senior neuropediatricians. Finally, the number of CP cases, in particular, infants born SGA, was limited despite the large background population, and the lack of statistical differences should therefore be interpreted with care.

In the current study, the overall proportion of children with a possible intrapartum origin of CP was \(~\)10%. This proportion is slightly larger than the 5% reported by Wu et al\(^{19}\) and the 6% reported by Nelson and Grether,\(^20\) but significantly lower than the 20% to 28% reported in some previous studies.\(^{21,22}\)

The proportion of children with a probable intrapartum origin of their CP did not vary between SGA and non-SGA children. Thus, our results do not support several previous studies reporting that the association between CP and SGA was mainly due to adverse intrapartum events and suggesting an increased vulnerability of SGA children.\(^2\)–\(^4,23\) These studies were much smaller than the current study, and they mainly relied solely upon low Apgar score as an indicator of intrapartum stress (Westwood et al in 1983,\(^4\) Berg in 1988\(^2\) and 1989,\(^3\) and Taylor and Howie in 1989\(^23\)). However, placental abruption occurred more often as a possible intrapartum cause of CP among SGA infants than among non-SGA infants with low Apgar scores in our study. This suggests that SGA children may be more vulnerable to
placental abruption or that causal factors underlying IUGR and placental abruption may be related, although this should be interpreted with caution because of small numbers.

Another potential explanation of the lack of difference between the SGA and non-SGA group could be that more SGA newborns died in the neonatal period. We found some evidence in favor of this explanation (Table 2), but the difference in neonatal death was borderline, not statistically significant ($P = .07$), and disappeared when congenital malformations (ie, the main cause of death in the neonatal period among term born) were excluded. Thus, among SGA children without congenital malformations, neither the risk of neonatal death nor CP differed from that of non-SGA children (Table 2).

In contrast, the vast majority of CP children born SGA most likely had an antenatal origin to their CP. The most prevalent antenatal risk factors were congenital malformations, maternal disease (unspecified), and abnormal presentation. Congenital malformations are a well-known cause of fetal growth restriction, and several studies have shown that malformations, irrespective of being a central nervous system malformation or not, are associated with CP. Maternal diseases, including pre-eclampsia and maternal hypothyroidism, can lead to growth restriction in utero, although they may affect brain development differently. However, the numbers in our study were too small to study specific maternal diseases. Likewise, abnormal presentation of the fetus at birth may be regarded as a potential result of being growth retarded as well as the result of a brain insult or a congenital malformation. All these conditions were more common among SGA than among non-SGA children, but did not differ between children with CP. Thus, our results suggest that the increased risk of CP among children born SGA is probably not caused by 1 or 2 single risk factors, but more likely by a higher occurrence of all risk factors in this group.

With regard to the biological plausibility of an antenatal cause of CP in children born SGA, both IUGR and brain injury might have a common antenatal pathway, for example, with chronic intraventricular hypoxia or intrauterine infections causing both brain injury and IUGR. In a recent article, Guo et al (2010) suggested that chronic intraventricular hypoxia may induce a fetal adaptive response causing brain injury. Accordingly, they argue, this may explain why induction of labor does not improve neurologic outcome in IUGR fetuses, because the brain injury in these children would already be established. Furthermore, poor growth may cause CP or other conditions (eg, hypoglycemia) responsible for CP or an antenatal brain injury may cause poor growth, for example, through endocrine pathways.

The subgroup analyses of children with MRI supported the interpretation that the brain injuries leading to CP both in SGA and non-SGA children mainly are of antenatal origin. The most common finding both among SGA (41%) and non-SGA (29%) children was periventricular white matter injury. Consistently with Volpe, these findings suggest that maternal and fetal infections or inflammation may be significant antenatal contributing factors of CP. Our finding among SGA children is consistent with Wu et al, who found that IUGR mainly was associated with periventricular white matter injury, which they, by using the first percentile as cutoff, reported in 5 of 13 (38%) cases. Moreover, Wu et al reported that none of the growth-restricted infants in their study had neuroimaging findings suggestive of perinatal hypoxia-ischemia, indicating that CP in SGA children is most often related to an antenatal event. In our study, 14% of the SGA children had basal ganglia injury (with and without cortical injury/white matter injury), which may be suggestive of perinatal hypoxia-ischemia. However, taking into consideration Apgar score, known risk factors, and subtype of CP, only 2 of 5 cases with basal ganglia injury were considered to be of intrapartum origin.

CONCLUSIONS

Our results, supported by MRI, suggest that the vast majority of SGA children with CP have an antenatal brain injury and that the role of intrapartum events in the etiology of CP in SGA children is not different from its role in the non-SGA population. This finding could not be completely explained by a higher neonatal mortality of SGA newborns experiencing perinatal stress.

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