Functional Outcomes at Age 7 Years of Moderate Preterm and Full Term Children Born Small for Gestational Age

Jozien C. Tanis, BSc[1], Koenraad N. J. A. Van Braeckel, PhD[1], Jorien M. Kerstjens, MD, PhD[1], Inger F. A. Bocca-Tjeertes, MD, PhD[1], Sijmen A. Reijneveld, MD, PhD[2], and Arend F. Bos, MD, PhD[1]

Objective To compare functional outcomes of 7-year-old (school-age) children born small for gestational age (SGA; ie, a birth weight *z* score ≤ −1 SD), with appropriate for gestational age (AGA) peers, born moderately preterm or full term.

Study design Data were collected as part of the Longitudinal Preterm Outcome Project study, a community-based, prospective cohort study of 336 AGA and 42 SGA born children (median gestational age 35 weeks, range 31-41). Of the SGA children, 32 were moderately preterm, 10 were full term; of the AGA, these numbers were 216 and 120, respectively. At 6.9 years, we assessed intelligence, verbal memory, attention, visuomotor integration, and motor skills and we collected the parent-reported executive functioning. We compared the outcomes of the SGA children with those of their AGA peers.

Results The performance of SGA children was similar to that of their AGA peers, except for attention control which was abnormal more often in SGA children (OR 3.99, 95% CI 1.32-12.12). The IQ of SGA children was 3 points lower, but this difference failed to reach significance.

Conclusions At school age, children born SGA have a greater risk of abnormal test scores on attention control than children born AGA, independent of gestational age. Their motor and many other cognitive functions are similar. The impact of these outcomes seems limited. Nevertheless, the consequences for school performance deserve attention. *(J Pediatr 2015;166:552-8)*.

An infant born small for gestational age (SGA) is considered to be at risk of impaired development in childhood.[1] Reports on the outcomes of SGA-born children vary from minor to major deficits in comparison with their appropriate for gestational age (AGA) peers.[2-7] These deficits may lead to impaired neurocognitive outcome at school age.[8]

Another risk factor associated with impaired neurodevelopmental outcomes is preterm birth.[9,10] Very preterm birth (<32 weeks' gestational age [GA]) can cause serious perinatal complications and neurodevelopmental sequelae.[11] The combination of very preterm birth and born SGA, poses an additional risk,[12] but to what extent is still under debate. Previously, with another cohort, we found that children born very preterm and SGA have poorer total and fine motor skills, selective attention, and visual perception compared with their very preterm, AGA peers.[13] Another study showed lower intelligence in the very preterm SGA children.[14]

The majority of SGA children, however, are born moderately preterm (MPT) or full term rather than very preterm. As with being born SGA, MPT birth also appears to be a risk factor associated with impaired outcome.[15-18] The additional effects, however, of SGA birth in MPTs and full terms on neurodevelopment are not yet understood. Previous studies on functional outcomes of MPT and full-term SGA children reported conflicting results.[19-21] Differences in outcomes may be the result of the variety of subgroups, the definition of SGA, the inclusion of preterm-born or full term-born children, or to the fact that most were single-center studies. Because our study group is a community-based cohort, our findings might add to the knowledge on neurodevelopment of MPT and full term-born SGA children. Our aim was, therefore, to compare the functional outcomes of 7-year-old (school-age) MPT and full term children born SGA with that of their AGA peers in a community-based cohort, while taking into account sex and GA.

Methods

This study was part of the Longitudinal Preterm Outcome Project, a study on growth, development, and general health of preterm-born children.[22] Children

AGA	Appropriate for gestational age
GA	Gestational age
IUGR	Intrauterine growth restriction
Movement ABC	Movement Assessment Battery for Children
MPT	Moderately preterm
SGA	Small for gestational age

From the [1]Neonatology, Beatrix Children's Hospital, and [2]Department of Health Sciences, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Supported by the foundation of Beatrix Children's Hospital, the Cornelia Foundation for the Handicapped Child, A. Bulk-Children Preventive Health Care Fund (KS 15F07(2).59), Dutch Brain Foundation, FrieslandCampina, Friso Infant Nutrition, and Pfizer Europe. The authors declare no conflicts of interest.

Registered with Controlled-Trials.com: ISRCTN80623320.

http://dx.doi.org/10.1016/j.jpeds.2014.11.043

were recruited from 13 Dutch Preventive Child Health Care Centers at the age of 4 years. From this community-based cohort of 45 446 children born during 2002 and 2003, all 1843 preterms (<36 weeks' GA) and a matched random sample of 674 full terms (38-41^{+6} weeks' GA) were included. The matched full-term group comprised the first subsequent child from the same birth year as a preterm born child with a GA between 38^{+0} and 41^{+6} weeks that was filed after each second preterm child. The GAs were calculated from the date of last menstruation, and in the majority of cases confirmed by early ultrasound measurements. We excluded children with major congenital malformations, congenital infections, or syndromes.

At 7 years of age, we invited all children from the cohort to participate who had participated at the age of 4 years and who were living in the 3 northern provinces of The Netherlands (Groningen, Friesland, and Drenthe): 341 MPTs (32-35^{+6} weeks' GA) and 195 full terms (38-41^{+6} weeks' GA). The parents of 93 MPT children and 65 full-term children could not be traced or they declined to participate in the follow-up, leading to a participation percentage of 71%. We found no significant differences between the outcomes of children who participated in the present study and those who dropped out. Altogether, 248 born MPT (138 boys, 110 girls, median GA 34 weeks) and 130 full-term children (58 boys, 72 girls, median GA 40 weeks) participated in our study.

For the present study, we used the same cohort to compare the functional outcomes of MPT and full-term children born SGA with those of their AGA peers. We categorized the MPT and full-term children into 1 of 2 groups: birth weight < -1 SD and birth weight > -1 SD according to GA using the Dutch Kloosterman curve.[23] We took a somewhat lower cut-off for SGA (-1 SD, below the 16th percentile) according to the findings of the Etude Epidémiologique sur les Petits Ages Gestationnels study,[24] and also to increase the power of potential differences between the groups. We denoted the study group (birth weight < -1 SD) as SGA. Of 42 SGA children 32 (76%) were MPT, and 10 (24%) were full term. Eighteen of the 32 MPT and 5 of the 10 full-term children were below the 10th percentile.

Medical data were extracted from hospital charts. The study was approved by the Ethics Review Board of University Medical Center Groningen. Examinations were performed in accordance with the institutional and international ethical standards, with written informed consent from all parents.

Children and their parents were invited to visit University Medical Center Groningen or a well-baby clinic in their neighborhood for a 3-hour assessment comprising a number of standardized neuropsychologic tests and a questionnaire. Each child was tested individually by a trained psychologist, who was blind as to group assignment, whereas the parents completed the questionnaire in the waiting room.

Cognitive Outcomes

We assessed cognitive outcomes by using several standardized tests. A short form of the Wechsler Intelligence Scale for Children, Third Edition, Dutch version was used to determine intelligence.[25,26] We calculated total IQ on the basis of the verbal and performance IQ subtests. We measured selective attention and attention control with "Map Mission" and "Opposite Worlds," 2 subtests of the Test of Everyday Attention for Children.[27] Selective attention refers to a child's ability to select target information from an array of distractors. Attention control refers to the ability to shift attention flexibly and adaptively. To assess verbal memory, we used Rey's Auditory Verbal Learning Test.[28] It consists of a 15-word list that is repeated to the child 5 times. After each trial, we tested immediate recall. Delayed recall was assessed after an interval of 20 minutes. To assess visuomotor integration, we used "Design Copying" of the Neuropsychological Assessment, Second Edition.[29] Visuomotor integration involves the integration of visual information with finger-hand movements.

We used the Behavior Rating Inventory of Executive Function questionnaire,[30] which was filled out by the parents, to assess executive functioning in daily life. We transformed the percentile rank scores (high percentile means poor outcome) of the global executive composition score into percentiles (low percentile means poor outcome). We did this to present all outcome measures in the same way.

Motor Outcome

We used the Movement Assessment Battery for Children (Movement ABC)[31] to assess motor outcomes. This is a standardized test that measures total motor performance based on subscores using Dutch norms for manual dexterity (fine motor skills), ball skills, and static-dynamic balance (coordination). The greater the score, the poorer the outcome.

Statistical Analyses

MPT and full-term groups were combined for analyses. We tested the differences in patient demographics between SGA and AGA groups with the Mann-Whitney U test or the χ^2 test where appropriate. Regarding functional outcomes, we tested differences in continuous outcome scores between the SGA and AGA groups by multiple linear regression analyses. Next, we adjusted for GA (MPT/full term), sex, and assessed the interaction of SGA/AGA by GA category. GA was dichotomized as to avoid the assumption of exponential associations between determinant and outcome, a peculiarity of the logistic model. Second, we classified functional outcomes into 3 categories; normal (>15th percentile, IQ $\geq$85), borderline (5-15th percentile, IQ 70-84), and abnormal (<5th percentile, IQ <70). The motor outcome classification was based on the Dutch norms in the manual. Third, we calculated OR via multiple logistic regression analyses and investigated OR for borderline/abnormal vs normal and for abnormal vs normal/borderline outcomes. Next, we adjusted for GA and sex, and again assessed the interaction of SGA/AGA with GA category. We adjusted for GA and sex as these may act as confounders even if they do not differ with statistical significance between the 2 groups.