Original Article

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Neurological Outcome in Preterm Small for Gestational Age Infants Compared to Appropriate for Gestational Age Preterm at the Age of 18 Months: A Prospective Study

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The aim of this study was to investigate the neurological outcome of premature small for gestational age infants at the corrected age of 18 months by the Hammersmith Infant Neurological Examination. A prospective trial was conducted comparing 41 preterm infants being small for gestational age with 41 appropriate for gestational age infants. Birth weight was significantly lower in small for gestational age infants compared with appropriate for gestational age infants (1724.6 $\pm$ 433 versus 1221 $\pm$ 328 g). There were no significant differences regarding the median gestational age and Apgar scores. Median global scores differ significantly between both groups: 75 (47-78) versus 76 (72-78) for the small for gestational age and appropriate for gestational age infants, respectively. Both groups had optimal scores. In conclusion, although the small for gestational age group scored lower in the Hammersmith Infant Neurological Examination, median global score in both groups was within optimal range.

Keywords: small for gestational age; intrauterine growth restriction; Hammersmith Infant Neurological Examination; preterm infant; neurological outcome

Intrauterine growth restriction is a multifaceted condition that results in the birth of a small for gestational age infant ($\leq$10th percentile) and has been associated with increased short and long-term risk.[1-8] Small for gestational age and intrauterine growth restriction are not synonymous terms. The term small for gestational age refers to the size of the infant at birth, whereas the term intrauterine growth restriction suggests diminished growth velocity in the fetus as documented by at least 2 intrauterine growth assessments.[9,10] The condition of intrauterine growth restriction differs from prematurity per se, but they often coexist, and may explain the resulting poor outcome in such growth-compromised infants. Intrauterine growth restriction results from various maternal and fetal disorders. Although the underlying mechanisms for intrauterine growth restriction are heterogeneous,[11,12] the most common cause is uteroplacental dysfunction, which restricts the delivery of critical amounts of vital substances to the fetus via the placenta.[13,14] A suboptimal supply of nutrients in utero is a likely cause of reduced fetal and brain growth.[15-17] Different response patterns of brainstem auditory evoked potential have been noted in preterm intrauterine growth restriction infants compared with appropriate for gestational age infants.[18] Accordingly, Bos et al[19] showed that preterm small for gestational age infants had less mature spontaneous leg movements. However, Vermeulen et al[20] reported restricted intrauterine growth not to be a risk factor for adverse developmental outcome. In addition,

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Gortner et al[21] found no significant differences regarding neurodevelopmental outcome between preterm small for gestational age and appropriate for gestational age infants.

Therefore, studies investigating the neurodevelopmental outcome of infants being born small for gestational age compared with those being born appropriate for gestational age show conflicting results.[21] This might be explained by different definitions of restricted intrauterine growth, by different pathophysiologies underlying restricted intrauterine growth, and by different methods used to evaluate the neurodevelopmental and neurological outcome.

The Hammersmith Infant Neurological Examination is a simple and scorable method for examining infants between 2 and 24 months of age.[22] This assessment and the obtained optimality scores were recently standardized in a low-risk population[23] and in healthy term infants between 12 and 32 weeks of age.[24] The examination has also been validated in a population of term infants who had perinatal asphyxia[25] and recently has been standardized in very preterm infants between 6 and 15 months corrected age.[26] The optimality scores have been developed on the basis of the frequency distribution of the findings for each item.

As such, the present study was designed to examine the neurological outcome of premature small for gestational age infants at the corrected age of 18 months. We hypothesized that at 18 months corrected age preterms being born small for gestational age would display lower neurological outcome than appropriate for gestational age preterms. It was further hypothesized that small for gestational age infants would score less optimal in the subsections from the Hammersmith Infant Neurological Examination.

Materials and Methods

Participants were all preterm infants with a gestational age below 34 weeks being born from January 2005 to January 2006 and discharged from our level III neonatal intensive care unit. The study sample group 1 included 41 small for gestational age infants (birth weight $\leq$10th customized centile)[27] who were matched to a control group 2, which included 41 appropriate for gestational age infants whose birth weight was between the 10th and 90th customized centile[27] who were born within the same year and whose gestational age was within the same week to the respective small for gestational age infant. Gestational age was determined from the date of the last menstrual period when that was reported as "normal" and was confirmed by sonographic measurement of crown-rump length during the first trimester of pregnancy. Birth weight was measured with an electronic scale.

Exclusion criteria included genetic or syndromic disease, gross chromosomal abnormalities, and intraventricular hemorrhage grade 4.

The following variables were recorded prospectively: gestational age, birth weight, Apgar scores, preeclampsia, antenatal steroids exposure, mode of delivery, respiratory distress syndrome, need for surfactant administration, patent ductus arteriosus,[28] necrotizing enterocolitis, intraventricular hemorrhage,[29] periventricular leukomalacia,[30] bronchopulmonary dysplasia, and retinopathy of prematurity and days of hospitalization.

Table 1. Items Examined From the Hammersmith Infant Neurological Examination

Section1: Neurological Examination
Assessment of cranial nerve function
Facial appearance, eye appearance, auditory response and visual response, sucking/swallowing
Posture of
Head, trunk, arms, hands, legs, feet
Movements
Quantity/quality
Tone
Scarf sign, passive shoulder elevation, pronation/supination, adductors, popliteal angle, ankle dorsiflexion, pulled to sit, ventral suspension
Reflexes and reactions
Tendon reflexes, arm protection, vertical suspension, lateral tilting, forward parachute

Infants were scheduled to be seen at 18 months corrected age. At this appointment, Hammersmith Infant Neurological Examination was performed after a standardized physical examination. All infants were assessed by both a trained neonatologist and a pediatric physiotherapist. Romeo et al,[31] in a recently published article, conclude that this scoring system should complement other clinical and instrumental examinations in follow-up programs. The optimality score is based on the frequency distribution of the scores in a low-risk normal term population at 12 and 18 months of age. The test includes 26 items assessing cranial nerve function, posture, movements, tone, and reflexes (Table 1). Each item is scored separately, and the scores can be added to achieve a global optimality score. In the follow-up visit, parents reported about motor milestones of development such as head control, sitting, voluntary grasp, ability to kick in supine, rolling, crawling, standing, and walking as they described in section 2 from the Hammersmith Infant Neurological Examination.

Statistical Methods

The data were analyzed using the SPSS 11.5 statistical software. The relation between categorical variables was investigated using χ^2 or Fisher exact tests. To determine the relation between continuous variables, the Mann-Whitney or the t test was used depending on the distribution. To prove correlations between test results and basic characteristics of study infants, the Spearman rank correlation coefficient was used. A difference in statistical significance was considered if P value was $<.05$. The study was approved both by hospital's and by university's ethical committees.

Results

Characteristics of Population

Fifty-three small for gestational age infants were enrolled and matched with 53 appropriate for gestational age infants. A total of 41 small for gestational age infants and

Table 2. Basic Perinatal and Neonatal Characteristics of Study Infants

	SGA Infants (n = 41)	AGA Infants (n = 41)	*P* Value
Gestational age (weeks)[a]	32 (26-34)	32 (26-34)	ns
Birth weight (g)[b]	1221.46 (328.34)	1701.53 (429.41)	<.0001
Customized birth weight centile[a]	0.00 (0.00-8)	39 (11-88)	<.0001
Height (cm)[b]	38.24 (4.16)	42.33 (3.68)	<.001
Head circumference (cm)[b]	27.90 (3.35)	29.58 (2.57)	.035
Gender (male), n (%)[c]	21 (51.20)	21 (51.20)	ns
Mode of delivery (caesarean section), n (%)[c]	33 (80.50)	30 (73.20)	ns
Apgar scores 1 minute[a]	7 (3-8)	8 (4-8)	ns
Apgar scores 5 minutes[a]	8 (7-10)	9 (7-10)	ns
Conception-IVF, n (%)[d]	20 (48.80)	22 (53.70)	ns
Preeclampsia, n (%)[d]	13 (31.70)	3 (7.30)	<.0001
Prenatal steroids, n (%)[c]	32 (78)	33 (80.50)	ns

Note: AGA, appropriate for gestational age; IVF, in vitro fertilization; SGA, small for gestational age.
a. Mann-Whitney *U* test was used; data presented as median (range).
b. The *t* test was used for probability value; data presented as mean ± SD.
c. Fisher exact test was used; data presented as n (%).
d. χ^2 exact test was used; data presented as n (%).

41 appropriate for gestational age infants could be included in the follow-up examination at a corrected median age of 17.7 months (ranged from 15.8 to 23.8) for the small for gestational age group and 17.8 months (ranged from 16.21 to 23.4) for the appropriate for gestational age group.

The characteristics of study infants are given in Table 2. As expected, the incidence of preeclampsia was greater in the mothers of small for gestational age infants ($P < .0001$). Apgar scores at 1 and 5 minutes were without any statistical difference. There were 21 boys and 20 girls in each study group. The median (range) gestational age in both groups was 32 (26-34) weeks. Mean (±SD) birth weight was 1221 (±328) g and 1724 (±433) g for small for gestational age and appropriate for gestational age infants, respectively ($P < .0001$). Birth weight–customized centiles were significantly lower in small for gestational age group ($P < .0001$). Length and head circumference were significantly lower in the small for gestational age group ($P < .001$ and $P = .035$, respectively). The incidence of respiratory distress syndrome and the need for surfactant administration were higher in appropriate for gestational age infants ($P = .056$ and $P = .002$, respectively). Duration of hospital stay was significantly higher in the small for gestational age group ($P = .005$). During the neonatal period, no differences were observed concerning the incidence of bronchopulmonary dysplasia, intraventricular hemorrhage, and periventricular leukomalacia. An overview is given in Table 3.

Hammersmith Infant Neurological Examination Testing

Function of cranial nerves. There was no significant difference between small for gestational age and appropriate for gestational age infants in the subscores for this section. The small for gestational age group had a median score of 15 (ranged from 9 to 15), while the appropriate for gestational age group had a median score of 15. A score of 15 was regarded as optimal and a score below 15 as suboptimal (maximum score possible, 15; Table 4).[23]

Posture. The subscores for posture were significantly lower ($P = .004$) in the small for gestational age group with a median of 17 (ranged from 8 to 18). The appropriate for gestational age group had a median score of 18 (ranged from 14 to 18). The scores between 16 and 18 were regarded as optimal and below 16 as suboptimal (maximum score possible, 18).[23]

Movements. No statistically significant differences could be observed between 2 groups in the subscores for movement. Small for gestational age infants had a median score of 6 (ranged from 4 to 6), and the appropriate for gestational age infants had a median score of 6 (maximum score possible, 6). A score of 6 was regarded as optimal and all the others as suboptimal.[23]

Tone. There were no statistically significant differences in the subsores of tone subsection between small for gestational age (median 23, ranged from 15 to 24) and appropriate for gestational age (median 24, ranged from 18 to 24) groups. The scores between 22 and 24 were regarded as optimal and all those below 22 as suboptimal (maximum score possible, 24).[23]

Reflexes and reactions. The subscores for this subsection were without statistical difference. The small for gestational age group had a median of 15 (ranged from 9 to 15), while the appropriate for gestational age group had a median of 15 (ranged from 12 to 15). The scores

Table 3. Complications During the Neonatal Period

	SGA Infants (n = 41)	AGA Infants (n = 41)	*P* Value
Respiratory distress syndrome, n (%)[a]	21 (51.20)	29 (70.70)	.056
Surfactant administration, n (%)[b]	24 (58.53)	29 (70.73)	.002
Bronchopulmonary dysplasia, n (%)[a]	8 (19.51)	3 (7.3)	.097
Intraventricular hemorrhage (2-3), n (%)[b]	2 (4.80)	4 (9.60)	.406
Periventricular leukomalacia, n (%)[a]	1 (2.40)	0	.500
Patent ductus arteriosus, n (%)[a]	3 (7.30)	5 (12.19)	.356
Necrotizing enterocolitis, n (%)[b]	3 (7.30)	0	.012
Retinopathy of prematurity > 3, n (%)[b]	1 (2.4)	0	.210
Nosocomial sepsis, n (%)[b]	13 (31.70)	11 (26.80)	.516
Hospital stay (days) [a]	46.12 (26)	30.73 (21)	.005

Note: AGA, appropriate for gestational age; SGA, small for gestational age.
a. Fisher exact test was used; data presented as n (%).
b. χ^2 exact test was used; data presented as n (%).

Table 4. HINE Scores in Study Infants[a]

	SGA Infants (n = 41)	AGA Infants (n = 41)	Optimal Score
Function of cranial nerves	15 (9-15)	15 (12-15)	15
Posture	17 (8-18)	18 (14-18)	16-18
Movements	6 (4-6)	6 (4-6)	6
Tone	23 (15-24)	24 (18-24)	22-24
Reflexes and reactions	15 (9-15)	15 (12-15)	13-15
Global score	75 (47-78)	76 (72-78)	74-78
Corrected postnatal age at follow-up	17.7 (15.8-23.8)	17.8 (16.2-23.4)	

Note: AGA, appropriate for gestational age; HINE, Hammersmith Infant Neurological Examination; SGA, small for gestational age.
a. Data presented as median and range.

between 13 and 15 were regarded as optimal and all those below 13 as suboptimal (maximum score possible, 15).[23]

Global score. There were statistically significant differences between 2 groups regarding the global score for section 1 from the Hammersmith Infant Neurological Examination ($P = .024$). Small for gestational age infants had a median global score of 75 ranged from 47 to 78, while appropriate for gestational age infants had a median score of 76 ranged from 72 to 78 (maximum score possible, 78; Table 5). Based on frequency distribution, reported from previous studies, at 18 months a global score of 74 or above is regarded as optimal while scores below 74 as suboptimal.[23]

Motor outcome. No statistically significant differences could be observed between 2 groups regarding the motor milestones: head control—all the time maintained upright at 6 months for small for gestational age versus 5 months for appropriate for gestational age, stable sitting (median 8 months each), touches toes (median 6 months each), rolling supine to prone (7 months versus 6 months for appropriate for gestational age), crawling (median 9 months each), standing (median 12 months each), and walking (median 13 months each). All 41 children from the appropriate for gestational age group were able to walk independently by the age of 18 months. From the small for gestational age group, 5 children were unable to walk independently at 18 months corrected age and 1 of those was unable to sit. Of these 5 children, 1 had tetraplegia, 2 had hemiplegia, 1 had diplegia, and 1 was hypotonic.

Table 5. The Frequency Distribution of the Global Scores in Section 1 at 18 Months

Score AGA Infants (n = 41)	Frequency, n (%)	Score SGA Infants (n = 41)	Frequency, n (%)
47	0	47	1 (2.4)
55	0	55	1 (2.4)
61	0	61	1 (2.4)
62	0	62	1 (2.4)
67	0	67	1 (2.4)
68	0	68	1 (2.4)
70	0	70	2 (4.9)
71	0	71	2 (4.9)
72	3 (7.3)	72	3 (7.3)
73	2 (4.9)	73	2 (4.9)
74	5 (12.2)	74	1 (2.4)
75	4 (9.8)	75	5 (12.2)
76	7 (17.1)	76	7 (17.1)
77	4 (9.8)	77	3 (7.3)
78	16 (39)	78	10 (24.4)

Note: AGA, appropriate for gestational age; SGA, small for gestational age.

The rate of need for physiotherapy was higher in the small for gestational age group (20 small for gestational age infants needed physiotherapy versus 8 appropriate for gestational age infants). At the follow-up time, parents reported that their infants followed a Neurodevelopmental Treatment program, 2 to 3 times/week.

Discussion

In the current study, the Hanmmersmith Infant Neurological examination was applied at the corrected age of 18 months. We could demonstrate statistically significant

differences between small for gestational age and appropriate for gestational age infants. Although small for gestational age infants scored lower, their median global score was within optimal range. The subscores of posture were significantly lower for the small for gestational age group but still within the optimal range. In our study, 63.5% of the premature small for gestational age infants had optimal scores and 36.5% had suboptimal. In the appropriate for gestational age group, 87.8% of the premature infants had optimal scores while 12.2% had suboptimal. Moreover, 25% of the small for gestational age infants with independent walking at 18 months corrected age had a suboptimal score below 73 ranged from 68 to 73. Of the appropriate for gestational age infants, 12.5% had suboptimal scores between 72 and 73 although they could walk independently at the corrected age of 18 months. The items that were most frequently suboptimal in the small for gestational age group were maturational item, such as lateral tilting and items from tone subsection such as adductors and popliteal angle.

The infant from the small for gestational age group that scored 47 had tetraplegia, while the infant with a score of 55 had hemiplegia, and the infant with a score of 61 had mild hemiplegia, and this is in accordance with results reported by other authors.[31]

The factor of different degrees of immaturity in both groups has been excluded as we matched infants of the same gestational age. However, a small percentage of initially enrolled infants was lost on follow-up and therefore this factor is not likely to influence the results of the study. In advance, our study criteria minimized contamination of the results, as cases of perinatal asphyxia and major intraventricular hemorrhage were excluded. The incidences of neonatal neurological complications did not differ significantly between small for gestational age and appropriate for gestational age infants. Thus, this risk factor for poor neurological outcome was equally distributed. It must also be emphasized that every small for gestational age infant was the result of restricted intrauterine growth. These infants were classified as small for gestational age according to customized centiles[27] and therefore they represented the deviation from the genetical programmed potential leading to a deviation from the respective percentile. Previous studies showed restricted intrauterine growth not to be a risk factor for adverse neurodevelopmental outcome. This might be explained by the fact that they studied small for gestational age infants with weights as high as 2205 and 2295 g.[21,32] Our study population was distinctly lighter with maximum birth weight 1770 g.

Animal models have documented the impact of restricted intrauterine growth on fetal central system development and reported a reduction in brain neuronal number, neuronal migration to the cortex, and abnormalities in neuronal arborization and dendritic growth.[33-36] Between 26 and 34 weeks of gestation, the normal process of neuron loss and axon retraction is at its heights, with increased metabolic activity and increased vulnerability around the area of the basal ganglia, the caudate nucleus, the cerebellum, and the optic radiations. These areas are implicated in critical aspects of motor control.[37,38]

Using a case-matched design in which premature small for gestational age infants were matched for gestational age, it was found that small for gestational age as a group scored within optimal range. However, our results should be interpreted with caution because the ability to walk at 18 months corrected age does not exclude that some children, especially those with relatively low scores, might show significant differences more cognitive in nature, language delays, learning, and attention deficits at an older age. More research should be directed to this subgroup of premature infants, and their special neurodevelopmental needs to introduce early intervention programs before school age.

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