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Neurobehavior in Term, Small-for-Gestational Age Infants With Normal Placental Function

Francesc Figueras, Daniel Oros, Rogelio Cruz-Martinez, Nelly Padilla, Edgar Hernandez-Andrade, Francesc Botet, Carme Costas-Moragas and Eduard Gratacos

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WHAT'S KNOWN ON THIS SUBJECT: IUGR is associated with behavioral, sensorial, and cognitive dysfunctions in childhood and adolescence. Several studies on preterm infants correlated these difficulties with behavioral disruptions already present in the neonatal period.

WHAT THIS STUDY ADDS: This study extends the neurobehavioral effects of being SGA to term neonates with no signs of placental insufficiency, a subgroup of neonates traditionally considered to be at one end of the size spectrum of normal infants.

abstract

OBJECTIVE: The goal was to evaluate the neurobehavioral outcomes of term, small-for-gestational age (SGA) newborns with normal placental function.

METHODS: A cohort of consecutive term SGA newborns with normal prenatal umbilical artery Doppler ultrasound findings was created and compared with a group of term infants with size appropriate for gestational age, who were sampled from our general neonatal population. Neonatal behavior was evaluated at corrected age of 40 ± 1 weeks with the Neonatal Behavioral Assessment Scale. The effect of the study group on each Neonatal Behavioral Assessment Scale area was adjusted, through multivariate analysis of covariance, for smoking during pregnancy, maternal BMI, socioeconomic level, onset of labor, mode of delivery, use of epidural anesthetic medication, gestational age at delivery, postnatal age (in days) at evaluation, and gender.

RESULTS: A total of 202 newborns (102 SGA and 100 appropriate for gestational age) were included. All of the neurobehavioral areas studied were poorer in the SGA group, with significance for attention, habituation, motor, social-interactive, and regulation of state. The average mean differences in scores between the study groups were 0.77 (95% confidence interval: 0.38–1. 14) for attention, 0.64 (95% confidence interval: 0.13–1.14) for habituation, 0.52 (95% confidence interval: 0.31–0.74) for motor, 0.95 (95% confidence interval: 0.54–1.37) for social-interactive, and 0.68 (95% confidence interval: 0.23–1.13) for regulation of state. These differences remained significant after adjustment for potential confounders.

CONCLUSION: Term SGA newborns with no signs of placental insufficiency had poorer neurobehavioral competencies, which suggests delayed neurologic maturation. *Pediatrics* 2009;124:e934–e941

AUTHORS: Francesc Figueras, MD,[a,b,c] Daniel Oros, MD,[b] Rogelio Cruz-Martinez, MD,[b] Nelly Padilla, MD,[b] Edgar Hernandez-Andrade, MD,[b] Francesc Botet, MD,[b,c,d] Carme Costas-Moragas, PhD,[e] and Eduard Gratacos, PhD[a,b,c]

[a]Maternal-Fetal Medicine and [d]Neonatology Departments, Hospital Clinic, and [c]CIBER-ER, University of Barcelona, Barcelona, Spain; [b]Fetal and Perinatal Research Group, August Pi i Sunyer Institute for Biomedical Research, Barcelona, Spain; and [e]Department of Clinical and Health Psychology, Autonomous University of Barcelona, Barcelona, Spain

KEY WORDS

small for gestational age, intrauterine growth restriction, neurobehavioral outcome, Doppler ultrasonography

ABBREVIATIONS

SGA—small for gestational age
AGA—appropriate for gestational age
IUGR—intrauterine growth restriction
NBAS—Neonatal Behavioral Assessment Scale

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Address correspondence to Francesc Figueras, MD, Maternal-Fetal Medicine Department, Hospital Clinic, Barcelona, Spain. E-mail: ffiguera@clinic.ub.es

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Small for gestational age (SGA) and intrauterine growth restriction (IUGR) have been used interchangeably. The 2 terms are not synonymous, however; not all small newborns have IUGR, and not all infants with IUGR are small.[1] Most instances of true IUGR correspond to cases of placental insufficiency.[2] Intrauterine placental function evaluation through umbilical artery Doppler ultrasonography is the clinical standard used to distinguish between SGA and IUGR.[3–5] In addition, there is evidence that umbilical artery Doppler ultrasound use in these pregnancies improves a number of obstetric care outcomes and reduces perinatal deaths.[6] Although abnormal umbilical artery Doppler ultrasound findings are associated with adverse perinatal and neurodevelopmental outcomes,[7–10] small fetuses with normal umbilical artery Doppler ultrasound findings are considered to represent one end of the normal size spectrum, and the importance of treating them in a completely different manner, compared with infants with true IUGR, has been stressed.[11,12]

Many studies have found associations between prematurity with IUGR and later behavioral,[13–15] sensorial,[16,17] and cognitive[18–21] dysfunctions. Long-term outcomes for such infants reveal a specific profile of neurocognitive difficulties, with poor executive functioning, cognitive inflexibility, poor creativity, and language problems.[18,19] Other studies also reported long-term cognitive disadvantages for term SGA infants.[22,23] Some studies on preterm infants with IUGR correlated these difficulties during childhood with behavioral disruptions already present in the neonatal period,[13,14,24] a time when environmental influences are still minimal. Behavioral competencies in newborns are mainly related to neurologic maturation, and increasing evidence supports a neurobiological basis for infant behavior.[25] Furthermore, several studies demonstrated correlations between neonatal neurobehavioral skills and later neurocognitive development for preterm[13,14,24] and term[26,27] infants. There is no information on the neonatal behavior of term SGA newborns with normal placental function.

Preliminary evidence suggested indirectly that a proportion of term SGA infants without Doppler ultrasound signs of placental insufficiency might have been exposed to mild hypoxia in utero,[8,28,29] but the effects of this on brain maturation have not been investigated. The hypothesis of this study is that term SGA infants with normal placental function might have neurobehavioral disruptions attributable to abnormal brain maturation. Accordingly, this study was aimed at evaluating the neurobehavior of term SGA newborns with normal placental function.

METHODS

Subjects

A cohort was created of consecutive, suspected SGA, singleton infants delivered at gestational ages of >37 weeks between November 2006 and August 2008, with confirmed birth weights of <10th percentile according to local standards.[30] Pregnancies were dated according to the first-trimester crown-rump length measurement.[31] Exclusion criteria included congenital malformations (including chromosomopathies and infections) and umbilical artery pulsatility index values of >95th percentile.[32] Control subjects were defined as singleton term infants with size appropriate for gestational age (AGA) (≥10th percentile, according to local standards[30]) and were sampled from our general neonatal population during the same period; they were matched with case subjects according to the date of delivery (±7 days). A total of 108 SGA newborns fulfilled the inclusion criteria and were matched with 108 AGA infants. The study protocol was approved by the ethics committee, and parents provided written informed consent.

Neurobehavioral Outcomes

Neurobehavioral performance was evaluated at corrected age of 40 ± 1 weeks with the Neonatal Behavioral Assessment Scale (NBAS),[33] which assesses both cortical and subcortical functions by evaluating 35 items; the items are rated on a scale of 1 to 9 (with 9 being the best performance) except for 8 curvilinear scale items, which, according to the manual, are rescored as linear on a 5-, 6-, or 8-point scale. Items are grouped into 6 clusters, including habituation (habituation to light, rattle, bell, and tactile stimulation of the foot), motor (general tone, elicited activity, spontaneous activity, and motor maturity), social-interactive (responses to visual, animate, and inanimate auditory stimuli and alertness), organization of state (irritability, state lability, maximal excitation, and reaction time), regulation of state (self-quieting and hand-to-mouth responses), and autonomic nervous system. The social-interactive cluster was subscored for visual and auditory stimuli. In addition, as reported recently by the authors of the NBAS,[34] an aggregation of individual items (alertness, quality of the alert responsiveness, and cost of attention) was used to evaluate the capacity of infant attention.

All evaluations were performed by 1 of 3 trained examiners accredited by the Brazelton Institute (Harvard Medical School, Boston, MA); they had been tested previously for reliability and achieved an interrater reliability level of >90%. The examiners were blinded to the study group and perinatal outcomes. Neonates were assessed in the afternoon, between feedings, in a small, semidark, quiet room with a temperature between 22°C and 27°C, in the presence of ≥1 parent.

Placental Function Assessment

In all cases, prenatal Doppler ultrasound examinations were performed by 1 of 3 experienced observers (Drs Figueras, Oros, and Cruz-Martinez), with an Acuson Antares Premium Edition ultrasound system (Siemens, Mountain View, CA) equipped with a 2.3- to 4-MHz transabdominal transducer. The umbilical artery pulsatility index was calculated from ≥3 consecutive waveforms obtained from a free-floating portion of the umbilical cord during the absence of fetal movement, at insonation angles of <30°. All case subjects underwent a Doppler ultrasound examination within 7 days after delivery.

Statistical Analyses

Student's *t* test for independent samples and Pearson's χ^2 test were used to compare quantitative and qualitative data, respectively. Multivariate analyses were conducted through multivariate analysis of covariance in which a model was run for each different set of skills (attention, habituation, motor, state organization, state regulation, and autonomic nervous system), with the study group included as a factor and the following variables as covariates: (1) smoking during pregnancy (no smoking, 1–9 cigarettes per day, or ≥10 cigarettes per day); (2) maternal BMI at booking; (3) low socioeconomic level (routine occupations, long-term unemployment, or never worked; United Kingdom National Statistics Socio-economic Classification); (4) onset of labor (spontaneous versus induction); (5) mode of delivery (vaginal delivery versus cesarean section); (6) number of doses of epidural anesthetic medication (bupivacaine, 1.2–1.8 mg) during labor (none, 1–3 doses, or ≥4 doses); (7) gestational age at delivery; (8) postnatal age (in days) at evaluation; and (9) gender. For each model, assumptions for the multivariate analysis of covariance were checked and the multivariate significance of the F value was assessed with Wilks' λ *P* value. Also, the η^2 value was provided, which could be interpreted as the proportion of the total variance of the dependent variables explained by each factor and covariate. To rule out an expectation bias, the association between birth weight and NBAS scores was evaluated through Pearson correlation within each study group. The software package SPSS 14.0 (SPSS, Chicago, IL) was used for the statistical analyses.

TABLE 1 Clinical Characteristics of the Population

	AGA (*N* = 100)	SGA (*N* = 102)	*P*[a]
Primiparity, %	61	67.6	.32
Nonwhite ethnicity, %	21.2	16	.34
Maternal age, mean ± SD, y	31.8 ± 4.9	33.6 ± 4.9	.79
Maternal age of <21 y, %	5	2	.28
BMI at booking, mean, kg/m²	23.4	21.9	.003
Low socioeconomic level, %[b]	31	52	.003
Smoking, %			
Nonsmoking	85	83.3	.75
1–9 cigarettes per d	12	5.9	
11–19 cigarettes per d	2	7.8	
≥20 cigarettes per day	1	2.9	
Alcohol consumption of >170 g/wk, %	5	3.9	.71

[a] Student's *t* test for independent samples or Pearson's χ^2 test.

[b] Routine occupations, long-term unemployment, or never worked (United Kingdom National Statistics Socio-economic Classification).

TABLE 2 Perinatal Outcomes for the Population

	AGA (*N* = 100)	SGA (*N* = 102)	*P*[a]
Gestational age at delivery, mean ± SD, wk	39.7 ± 1.1	38.5 ± 1.1	<.001
Epidural anesthesia, %	92	100	.004
Birth weight, mean ± SD, g	3338 ± 390	2354 ± 266	<.001
Birth weight percentile, mean ± SD	52.2 ± 26.6	3.3 ± 2.2	<.001
Head circumference, mean ± SD, mm	346 ± 12.5	325 ± 11.4	<.001
Male, %	50	56.9	.33
Cesarean section, %	25	35.5	.11
Labor induction, %	18	65.7	<.001
Operative delivery because of fetal distress, %	8	16.7	.06
5-min Apgar score of <7, %	0	0	
Umbilical artery pH of <7.15 at delivery, %	3.3	10.2	.07
Neonatal unit admission, %	0	3	.08
Neonatal unit stay length, mean ± SD, d	0 ± 0	0.7 ± 3	.025

[a] Student's *t* test for independent samples or Pearson's χ^2 test.

RESULTS

For all of the 216 included infants, a neurobehavioral assessment visit was scheduled at corrected age of 40 ± 1 weeks. Parents of 6 case subjects and 8 control subjects later declined to participate, leaving a final population of 202 infants (102 SGA and 100 AGA). The habituation area could not be assessed for 50 newborns (21 SGA and 29 AGA) because of the absence of a sleeping period during the evaluation.

Table 1 depicts the clinical characteristics of the population. It is noteworthy that the mothers in the SGA group had a lower body weight and more frequently were from a low socioeconomic level. There were no cases of drug consumption other than tobacco or alcohol. Table 2 shows the perinatal outcomes of the population. As expected, SGA newborns had a lower birth weight and a smaller head circumference. Delivery in the SGA group was at an earlier gestational age (SGA: 38.5 weeks; AGA: 39.7 weeks) and more

TABLE 3 NBAS Scores According to Study Group

	Score, Mean ± SD		P[a]
	AGA (N = 100)	SGA (N = 102)	
Attention	6.94 ± 1.3	6.17 ± 1.4	<.0001
Habituation[b]	6.94 ± 1.4	6.3 ± 1.7	.014
Motor	5.67 ± 0.8	5.15 ± 0.8	<.0001
Social-interactive	6.71 ± 1.4	5.76 ± 1.5	<.0001
Visual	6.71 ± 1.5	5.35 ± 1.8	<.0001
Auditory	7.03 ± 1.4	6.15 ± 1.6	<.0001
Organization of state	4.09 ± 0.8	4.02 ± 0.8	.48
Regulation of state	5.91 ± 1.6	5.23 ± 1.5	.003
Autonomic nervous system	7.23 ± 0.9	7 ± 0.99	.08

[a] Student's t test.
[b] N = 152 (81 SGA and 71 AGA).

frequently was induced. Operative delivery because of fetal distress was twice as frequent in the SGA group. Although no infants in the AGA group were admitted to the neonatal unit 3% in the SGA group were.

Neonatal neurobehavior was assessed at 7.8 ± 7.2 and 10.5 ± 9.6 days of life in the AGA and SGA groups, respectively. Table 3 and Fig 1 detail the neurobehavioral outcomes according to NBAS area. Interestingly, all of the neurobehavioral areas studied were poorer in the SGA group, with univariate significance being achieved for attention, habituation, motor, social-interactive, and regulation of state areas. As Table 4 shows, these differences remained significant after adjustment for potential confounders (smoking during pregnancy, maternal BMI, low socioeconomic level, onset of labor, mode of delivery, use of epidural anesthetic medication, gestational age at delivery, postnatal age at evaluation, and gender). Of these covariates, induction of labor and cesarean delivery significantly accounted for lower habituation scores; gestational age at delivery for higher habituation scores; low socioeconomic level for lower social-interactive scores; and age at NBAS evaluation for higher habituation and social scores. Within each study group, no significant correlations were observed between birth weight and any of the neurobehavioral scores,

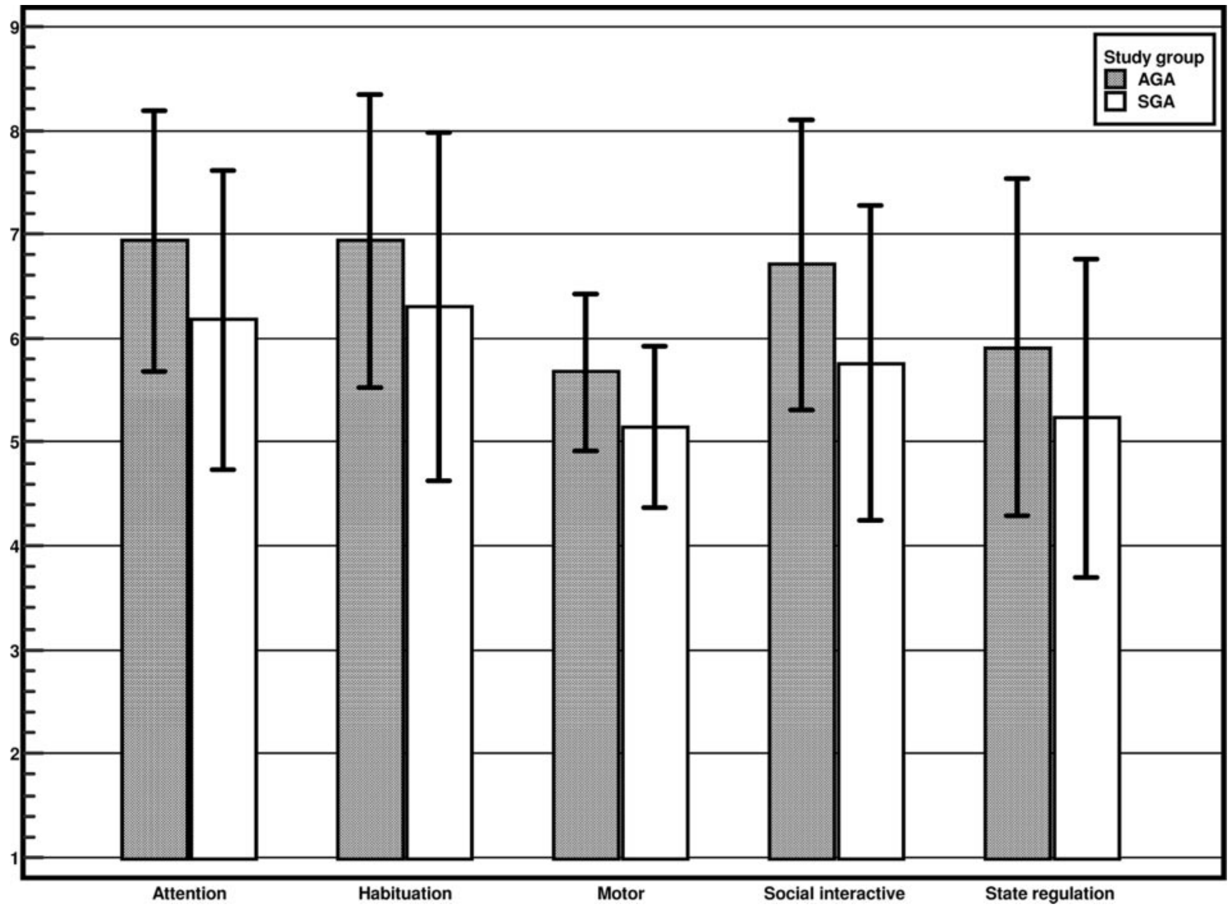

FIGURE 1
NBAS scores according to study group (mean and SD). Only significant associations are displayed (adjusted P value).

TABLE 4 Multivariate Analysis of Covariance Results

	F	P[a]	η^2, %
Attention			
SGA	5.96	.001	9.2
Cesarean delivery	2.14	.1	3.5
Age at NBAS evaluation[b]	1.9	.12	3.2
Habituation[c]			
SGA	4.59	.002	17
Smoking	1.03	.39	4.5
BMI[b]	0.73	.57	3.3
Labor induction	2.54	.046	10.4
Cesarean delivery	2.44	.05	10.1
Gestational age at delivery[b]	2.59	.04	10.6
Age at NBAS evaluation[b]	3.57	.01	14.1
Male	1.26	.29	5.5
Motor			
SGA	5.18	<.001	12.8
Smoking	1.16	.33	3.2
BMI[b]	1.13	.34	3.1
Labor induction	1.1	.36	3
Age at NBAS evaluation[b]	2.19	.06	5.8
Social-interactive			
SGA	4.6	<.001	18
Smoking	1.05	.4	4.8
BMI[b]	0.77	.61	3.6
Low socioeconomic level	2.49	.02	10.6
Epidural anesthetic medication	0.81	.59	3.7
Age at NBAS evaluation[b]	2.86	.008	12
Male	0.77	.61	3.6
Organization of state			
SGA	1.57	.18	3.4
Low socioeconomic level	2.16	.08	4.6
Regulation of state			
SGA	7.85	<.001	15.8
Autonomic nervous system			
SGA	2.14	.1	3.5
Smoking	2.5	.06	4

The adjusted effect of the study group (SGA versus AGA) on each NBAS area is shown. Adjustment for smoking during pregnancy, maternal BMI, socioeconomic level, onset of labor, mode of delivery, use of epidural anesthetic medication, gestational age at delivery, postnatal age at evaluation, and gender was performed. Covariates that explained >3% of the total variance of dependent variables (η^2) also are presented.

[a] Wilks' λ.

[b] Positive associations.

[c] $N = 152$ (81 SGA and 71 AGA).

except for organization of state ($R = 0.24$; $P = .03$) in the SGA group.

DISCUSSION

It is well known that premature SGA infants with abnormal umbilical artery Doppler ultrasound findings, as a surrogate sign of placental insufficiency, are at high risk of neurobehavioral and neurocognitive outcomes.[35–37] Our study extends the neurobehavioral effects of being SGA to term newborns with no signs of placental insufficiency, a subgroup of newborns traditionally considered to be at one end of the size spectrum of normal infants. Our findings challenge the concept that umbilical artery Doppler ultrasonography is a reliable tool to identify prenatally the constitutional term SGA infants at low risk. Subtle degrees of neurologic injury seem to occur before umbilical artery Doppler ultrasound waveforms become abnormal. In fact, animal[38] and mathematical[39] experimental models of placental vessel obliteration suggested that umbilical artery Doppler ultrasound findings become abnormal only in advanced stages of placental dysfunction.

Identifying at-risk infants is essential for understanding the association between fetal well-being and later neurodevelopmental problems and lays the basis for possible preventive interventions. Infant early temperament and behavior have been demonstrated to have an impact on breastfeeding during the first 6 months of life.[40] The poorer regulation and organization of state observed in our series and others[27] may negatively influence adherence to breastfeeding, which has been proved to be a protective mechanism with respect to neurodevelopmental outcomes at 2 years for SGA infants, independent of the presence of signs of placental insufficiency.[41] Therefore, promoting and supporting breastfeeding may be of special importance for these infants. In addition, because these infants are at risk of poorer neurodevelopmental outcomes, they might benefit from early educational interventions. Early educational interventions have been documented to improve cognitive outcomes[42] and, in some cases, to reduce antisocial behavior early in the school experience.[43] For low-risk premature infants, it has been reported that individualized developmental interventions prevent short-term neurobehavioral dysfunction.[44] It is not known whether interventions also could be effective for term SGA infants and would influence long-term outcomes.

We found poorer neonatal responses to both visual and auditory stimuli in SGA newborns. Long-term follow-up studies with preterm and term SGA infants found impaired processing of visual-spatial stimuli.[19] Animal models of chronic IUGR demonstrated reduced myelogenesis in the optic nerve[45] and reduced synaptogenesis in the visual cortex.[46] These factors could restrict the integration of cerebral cortical inputs. In addition, mistimed cell migration in premature infants could have an effect on synaptic plasticity, with functional and behavioral consequences.[47] Visual-spatial competencies also play a role in the neonatal capacity to select environmental stimuli to process and to act on, which provides important scaffolding on which attention skills are constructed through early childhood.[48]

IUGR also is associated with the development of attention-deficit/hyperactivity disorder symptoms in childhood and early adolescence.[49] Our finding of lower attention capacities in SGA newborn is in line with this finding. Two previous studies[13,24] found impaired attention skills among premature SGA infants. Structural correlations were made between attention scores and cortical gray matter[13] and hippocampal[24] volumes in the neonatal period. Whether NBAS findings predict attention later in childhood is not clear. However, some studies have found that, for term infants, attention is predictive of intelligence in childhood and adolescence.[50,51] A study of temperament in early infancy (5–6 months) performed with infants born at term reported significant prediction of attention deficits among 8-year-old children.[26]

There is substantial overlap between childhood attention disorders and the diagnosis of motor impairment, with poor movement skills.[52] Our finding of lower motor performance among SGA newborns is consistent with this association. With a series of 40 SGA premature neonates, Feldman and Eidelman[14] studied the correlation of neurobehavior with later cognitive function, as measured with the Bayley Scales of Infant Development. They found that neonatal motor maturity was correlated with Psychomotor Developmental Index values at 24 months.

Another interesting finding of our study was the lower level of self-regulation among SGA newborns, as reflected by the regulation of state NBAS cluster. For a series of 38 healthy term infants, Lundqvist-Persson[27] reported that levels of self-regulation were correlated with the infants' levels of cognitive development (personal-social development, speech development, and eye-hand coordination, subvariables in Griffiths' Mental Development Test) and with sleeping disorders at 2 years of age. We found no difference in autonomic nervous system functioning in SGA infants. This finding is consistent with previous studies that showed preserved sympathovagal balance in term SGA infants.[53] Autonomic nervous system problems are more likely to occur in preterm infants with acute and more-severe hypoxia.[54]

One strength of our study is that it included only term SGA infants without signs of placental dysfunction or congenital malformations, as low-risk SGA infants are defined in everyday clinical practice. No previous studies aimed at analyzing the effect of IUGR on neurobehavior reported the proportion of cases with placental insufficiency. This is a potential source of misinterpretation of results, because an unknown proportion of the newborns might have been exposed to a very prolonged period of intrauterine hypoxia. This study also has some limitations. Firstly, although NBAS assessment is a standard method for evaluating newborns' capacity to respond to the environment, reflecting brain maturation, it assesses only neurobehavior and not cognitive function.[55] However, several studies demonstrated correlations between neonatal neurobehavior and later neurocognitive development in preterm[13,14,24] and term[26,27] infants. Secondly, it could be argued the differences between SGA and AGA infants are likely to be clinically irrelevant, albeit statistically significant. However, because behavioral clusters are rated on a scale of 1 to 9, where 9 represents the best performance in some areas and 5 in others, a 1-point difference in absolute values represents a relative difference of 10% to 25%. Thirdly, it could be argued that the study design is prone to an expectation bias, because the examiners might have been influenced by the size of the infants during the neurobehavioral assessments. Within each study group, however, no significant correlations were found between birth weights and NBAS scores, except for organization of state in the SGA group. This makes it unlikely that this potential bias could explain the observed differences between SGA and AGA newborns in the other areas. In addition, our findings would be more valid if we had repeated the NBAS examinations to show that the behavior was consistent over time. Finally, mothers in the 2 study groups did not match with respect to sociodemographic conditions. It is likely that other factors associated with SGA also were different for these mothers. Although the effect of the study group on neurobehavior was adjusted with some of these potential confounders, we cannot rule out the possibility that some residual confounding is biasing our results.

CONCLUSIONS

We found poorer neurobehavioral competencies, suggesting delayed neurologic maturation, in a well-defined cohort of term SGA infants with no signs of placental insufficiency. Whether earlier markers of placental insufficiency or hypoxia could be used to identify high-risk infants and whether timely interventions for these infants could be of benefit require further investigation.

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