Being Small for Gestational Age Affect Neurodevelopmental Outcomes in Very Preterm Infants

Gestasyon Haftasına Göre Küçük Olmak Prematüre Bebeklerde Nörogelişimsel Sonuçları Olumsuz Etkiler

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Abstract

Introduction: There is insufficient data on neurodevelopmental outcomes of infants small for gestational age (SGA) with ≤30 weeks of gestation. The aim of our study was to compare the neurodevelopmental outcomes of preterm infants who are ≤30 weeks, in terms of being SGA or appropriate for gestational age (AGA).

Materials and Methods: The data of infants who were born at ≤30 GW, were evaluated retrospectively. Neurological examinations and developmental assessment using Bayley Scales of Infant Development 2nd edition was performed at the corrected age of 18-24 months.

Results: The data of 228 infants of whom 65 were SGA and 163 were AGA was evaluated in terms of neurodevelopment at the corrected age of 18-24 months. The mean gestational age (GA) was 28.4±1.1 in both groups (p=0.82) and the mean BW was 810±135 g in the SGA group and 1175±183 g in the AGA group (p<0.001). The SGA group had significantly lower Mental Development Index (p=0.01) and Psychomotor Development Index (p<0.001). In multivariate regression analysis, SGA was identified as an independent risk factor for neurodevelopmental delay (RR: 2.27; p=0.02).

Conclusion: Being SGA is a risk factor for neurodevelopmental impairment of preterm infants (≤30 GW).

Öz

Giriş: Gestasyon haftasına göre küçük (SGA) olan ≤30 hafta bebeklerin nörogelişimsel sonuçları hakkında yeterli veri bulunmamaktadır. Çalışmadaki amacımız SGA ve gestasyon haftasına göre normal (AGA) doğum ağırlığına sahip ≤30 hafta prematüre bebeklerde nörogelişimsel sonuçları karşılaştırmaktır.

Gereç ve Yöntem: Düzeltilmiş 18-24. aylarda nörolojik muayeneleri ve "Bayley Bebekler için Gelişimsel Değerlendirme Ölçeği II" ile gelişimsel değerlendirmeleri yapılan ≤30 hafta prematüre bebeklerin verileri retrospektif olarak değerlendirildi.

Bulgular: Düzeltilmiş 18-24. ayda SGA (n=65) ve AGA (n=163) gruplarında toplam 228 bebek nörogelişimsel açıdan değerlendirildi. SGA ve AGA grubunda ortalama gestasyon yaşı (sırasıyla 28,4±1,1 ve 28,4±1,1, p=0,82) ve doğum ağırlığı (sırasıyla 810±135 ve 1175±183 g, p<0,001) olarak tespit edildi. Nörogelişimsel değerlendirmede, SGA grubunda bilişsel ölçek puanı (p<0,01) ve hareket ölçek

puanı (p<0,001) anlamlı olarak daha düşük bulundu. Çok değişkenli lojistik regresyon analizinde SGA'nın nörogelişimsel gerilik için bağımsız risk faktörü olduğu saptandı (RR: 2,27, p=0,02).

Sonuç: Prematüre bebeklerin (≤30 hafta) gestasyon haftasına göre düşük doğum ağırlığı ile doğmaları, nörogelişimsel gerilik açısından risk faktörüdür.

Introduction

Prematurity is a major cause of neonatal morbidity and mortality resulting from anatomical and functional immaturity of the organ systems. Lower gestational age (GA) and/or birth weight (BW) lead to greater morbidity due to the higher degree of immaturity. Infants may have low BW for their GA due to maternal, placental, or fetal factors. Being small for gestational age (SGA) has been associated with numerous morbidities in term and preterm infants, and intensive care prognosis can be improved by a thorough knowledge of additional SGA-related problems of preterm infants, who already constitute a high-risk group (1,2).

Long-term follow-up of preterm infants has shown that as morbidities increase, neurodevelopmental outcomes are affected by numerous factors. The prevalence of neurodevelopmental anomalies in preterm infants with BW less than 750 g and 1500 g was reported as 50% and 10-20%, respectively, and BW and GA were identified as the main determinants of neurodevelopmental outcomes (3,4).

Neurological examination at 2 years of corrected age in 183 children born at extremely low BW revealed severe neurological sequelae in 20.6%, mild deficits in 18.7%, and normal neurological findings in 60.7%. The authors reported that GA was the most important factor impacting the development of neurological sequela in the long term (5). It was also shown that the first 2 years of life is most risky period in terms of complications of prematurity and requires close monitoring (6). Early diagnosis is critical for the treatment and rehabilitation of preterm infants.

Compared to appropriate for gestational age (AGA) infants, SGA infants have possible different growth patterns, adverse neurodevelopmental outcomes, and increased morbidity. Considering this, results related to both SGA and prematurity should be analyzed separately. Studies on neurodevelopmental outcomes of preterm SGA infants with ≤30 weeks of gestation are very few. While growth is one of the main goals in this particular group of premature infants, there is controversy regarding the neurodevelopmental outcomes. Therefore, there is a need to investigate the neurodevelopmental consequences of being premature and SGA in the childhood age group (7,8).

The aim of our study was to compare the long-term neurodevelopmental outcomes of preterm infants with ≤30 gestational weeks born SGA and AGA.

Materials and Methods

This retrospective cohort study included infants born before 30 weeks of gestation and followed up in a tertiary level neonatal intensive care unit (NICU) between 2015 and 2017. Neurodevelopmental testing was conducted at a corrected age of 24 months during follow-up in our center. Medical records were accessed from patient files and the hospital electronic database, retrospectively.

The study was approved by the Dr. Zekai Tahir Burak Women's Health Training and Research Hospital Ethics Committee (date: 29.05.2018, number:24/2018).

Demographic Characteristics

SGA was defined as BW below the 10th percentile for GA, AGA as BW between 10th and 90th percentile, and large for gestational age (LGA) as BW over the 90th percentile. Weight at birth was evaluated according to Fenton growth charts (9). GA at the time of birth was determined based on the mother's last menstrual period and the results of obstetric evaluation. Only AGA and SGA infants were included in the study. Children who had major congenital anomalies, who needed resuscitation in the delivery room, who died prior to neurodevelopmental assessment, or who had incomplete data were excluded.

The following data was obtained from the medical records: GA, BW, head circumference at birth, sex, maternal age, maternal hypertension and diabetes history, multiple pregnancy, antenatal steroid (ANS) use, mode of delivery, prolonged premature rupture of membranes (pPROM), first and fifth minute Apgar scores, respiratory distress syndrome (RDS; need for surfactant) (10), hemodynamically significant patent

ductus arteriosus (PDA; was diagnosed according to echocardiography performed between 24 and 72 hours (left atrium/aortic root >1.5 and/or ductus diameter >1.5 mm) (11), early-onset neonatal sepsis (ENS; sepsis on first 3 postnatal days) (12), culture-proven late-onset neonatal sepsis (LOS; sepsis after 3rd postnatal day) (13), necrotizing enterocolitis (NEC; was diagnosed according to laboratory, clinical, and radiological findings and was staged according to the modified Bell criteria, Bell stage ≥ IIb) (14), intraventricular hemorrhage (IVH; grade ≥3, cranial ultrasound imaging results were based on the worst finding at any given time for this patient before discharge) and periventricular leukomalacia (PVL) (15), oxygen levels, non-invasive respiratory support, mechanical ventilation (MV) durations, bronchopulmonary dysplasia (BPD; BPD was defined using the classification developed through a National Institutes of Health Workshop and reported by Jobe and Bancalari moderate/severe) (16), retinopathy of prematurity (ROP; was defined according to the International Classification of Retinopathy of Prematurity (ICROP) (17), postnatal corticosteroid treatment and length of NICU stay. These clinical and demographic characteristics were evaluated and compared between SGA and AGA patients.

Neurodevelopmental Evaluation

Developmental assessment was performed by developmental pediatrics specialist using the Bayley Scales of Infant Development II (BSID-II) at a corrected age of 18 to 24 months. Neurodevelopmental follow-up was conducted by a team consisting of a neonatologist, a developmental pediatrician, an audiologist, and an ophthalmologist.

Measures of neurodevelopmental outcomes included Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) with recommended adaptations for visual and auditory impairments. The mean BSID II score is 100 for MDI and PDI, with a standard deviation (SD) of 15; a score of less than 70 (42 SDs below the mean) indicates a significant delay. Infants who were so severely impaired that testing with the BSID II could not be performed were assigned an MDI and PDI score of 49 (18). 0 Neurodevelopmental impairment (NDI) was defined as the presence of any of the following: a) moderate-to severe cerebral palsy (CP; hypotonic,

spastic diplegia, hemiplegia, or quadriplegia) with functional deficits that required rehabilitative services, or b) bilateral hearing loss (requiring amplification) and/or blindness in either eye, or c) MDI or PDI scores <70 (19).

Sample Size

Sample size calculation was based on the morbidity variable. The power calculation was performed according to the data from a previous study which was conducted in the relationship of neonatal morbidity in SGA and AGA (20). The total sample size of 185 (61 for SGA group, 124 for AGA group) was sufficient to detect power of 80% and a significance level of 5%.

Statistical Analysis

SPSS® version 22.0 (IBM Corp, Armonk, NY) for Windows software was used for data analysis. Categorical variables were compared using chi-square test. Continuous data were summarized as mean and standard deviation and compared using Student's t-test. P values less than 0.05 were considered significant for all tests. Correlation analyses with MDI and PDI were performed using Pearson correlation tests. Multinomial logistic regression analysis was used to assess the effect of GA, BW, and other risk factors on NDI outcomes.

Results

Two hundred and eighty four patients with neurodevelopmental data were evaluated to be a participant of the study. Since 15 SGA and 41 AGA patients did not attend follow-up, their data was not available. These patients were excluded from the study. Therefore, a total of 228 SGA (n=65) and AGA (n=163) infants were evaluated in terms of neurodevelopment at the corrected age of 18-24 months, the flowchart of the patients was presented in Figure 1. The mean GA was 28.4±1.1 weeks in both groups (p=0.82) and the mean BW was 810±135 g in the SGA group and 1175±183 g in the AGA group (p<0.001). The median head circumference at birth was 24 (23.2-25.8) cm in the SGA group and 27 (26-28) cm in the AGA group (p<0.001). The groups were statistically similar in terms of sex, APGAR scores, rates of multiple pregnancy, antenatal steroid therapy and pPROM. Prevalence of preeclampsia and cesarean

delivery was significantly higher in the SGA group (p<0.05) (Table 1).

In terms of respiratory morbidities, SGA infants had higher surfactant requirement (61.5% vs. 47.8%; p=0.06) and significantly higher moderate/severe BPD incidence (15.3% vs. 2.4%; p=0.001), total duration of mechanical ventilation (median 1 day vs. 0 days; p<0.001), duration of noninvasive ventilation (median 6 days vs. 4 days; p<0.001), and duration of supplemental oxygen requirement (median 16 days vs. 6 days; p<0.001). The incidence of ENS, hsPDA, NEC, IVH, and ROP was similar between the groups, whereas culture-proven LOS was significantly more common among SGA infants (47.6% vs. 18.4%,

p<0.001). Moreover, SGA infants showed significantly higher rates of postnatal corticosteroid treatment, spontaneous intestinal perforation (SIP) and PVL incidences (p<0.05) (Table 2).

In neurodevelopmental assessment, the SGA group had significantly lower MDI [78 (56-92) vs. 84 (76-96); p=0.01] and PDI [74 (55-87) vs. 82 (73-94); p<0.001], and significantly higher incidences of NDI [25 patients (38.4%) vs. 32 patients (19.6%); p=0.003] and CP [6 patients (9.2%) vs. 4 patients (2.4%); p=0.03]. No differences were observed between the groups in terms of blindness or deafness (Table 3).

In multivariate regression analysis; grade III-IV IVH (RR: 9.85; p=0.002), GA (<28 weeks) (RR: 2.32;
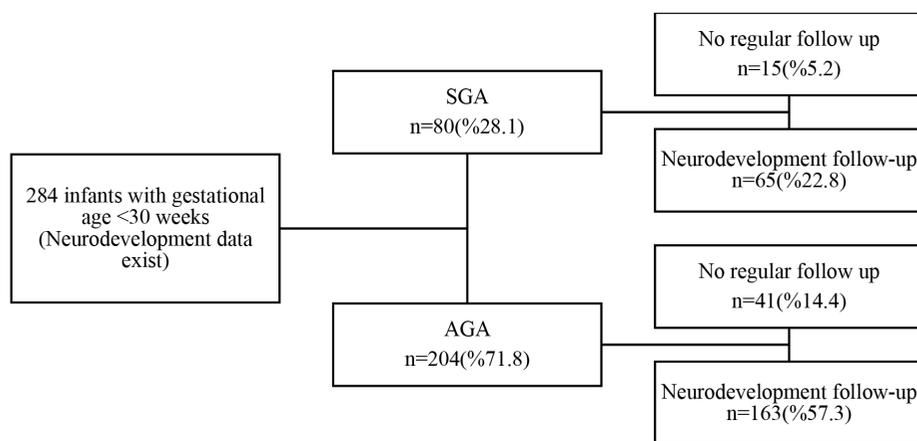
Figure 1. The flowchart of the patients.

SGA: Small for gestational age, AGA: Appropriate for gestational age

Table 1. Demographic features and neonatal outcomes			
Variables	SGA n=65	AGA n=163	p
Gestational age, weeks*	28.4±1.1	28.4±1.1	0.82
Birth weight, gram*	810±135	1175±183	**<0.001**
Head circumference at birth, cm†	24 (23.2-25.8)	27 (26-28)	**<0.001**
Male gender, n (%)	26 (40)	80 (49)	0.20
Cesarean delivery, n (%)	62 (95.3)	126 (77.3)	**0.01**
APGAR score at 5 minute†	8 (7-8)	8 (7-8)	0.08
Multiple pregnancy, n (%)	9 (13.8)	27 (16.5)	0.61
Antenatal corticosteroid, n (%)	52 (80)	115 (70.5)	0.14
pPROM, n (%)	8 (12.3)	20 (12.2)	0.99
Preeclampsia, n (%)	35 (53.8)	25 (15.3)	**<0.001**
*Mean ± standard deviation, †Median (interquartile range) p<0.05 was considered significant (in bold) SGA: Small for gestational age, AGA: Appropriate for gestational age, pPROM: Prolonged premature rupture of membranes			

p=0.02), being SGA (RR: 2.27; p=0.02), postnatal corticosteroid treatment (RR: 2.62; p=0.03) and, antenatal corticosteroid treatment (RR: 0.40; p=0.01) were identified as an independent risk factors for neurodevelopmental delay (Table 4).

Discussion

This study showed that being SGA alone was associated with poor neurodevelopmental outcomes at the corrected age of 18-24 months in preterm infants.

Moreover, being SGA is also associated with poor obstetric and fetal outcomes in preterm infants. Our evaluation of respiratory morbidities in the SGA group demonstrated higher surfactant requirement, longer durations of noninvasive and mechanical ventilation, and a greater prevalence of moderate/severe BPD in these infants.

Previously it was believed that with the effect of stress response and because of an unfavorable intrauterine environment, SGA infants would exhibit rapid lung maturation and RDS would decrease.

Table 2. Morbidities in the study group			
Variables	SGA n=65	AGA n=163	p
RDS, surfactant requirement, n (%)	40 (61.5)	78 (47.8)	0.06
hsPDA,requiring medical treatment, n (%)	23 (35.3)	62 (38)	0.70
Early onset neonatal sepsis, n (%)	9 (13.8)	25 (15.3)	0.77
Culture-proven late onset neonatal sepsis, n (%)	31 (47.6)	30 (18.4)	**<0.001**
Spontaneous intestinal perforation, n (%)	5 (7.6)	0 (0)	**0.002**
Necrotizing enterocolitis ≥ stage II, n (%)	4 (6.1)	2 (1.2)	0.06
IVH> grade II, n (%)	7 (10.7)	7 (4.2)	0.12
Periventricular leukomalacia, n (%)	8 (12.3)	4 (2.4)	**0.005**
Total duration of MV, day*	1 (0-5)	0 (0-2)	**<0.001**
Total duration of NIV, day*	6 (3.5-11)	4 (2-7)	**<0.001**
Supplemental oxygen requirement, day*	16 (5.5-27)	6 (3-15)	**<0.001**
Postnatal corticosteroid treatment, n (%)	12 (18.4)	13 (7.9)	**0.02**
BPD, moderate-severe, n (%)	10 (15.3)	4 (2.4)	**0.001**
ROP, laser treatment needed, n (%)	10 (15.3)	14 (8.5)	0.81

*Median (interquartile range)
p<0.05 was considered significant (in bold)
SGA: Small for gestational age, AGA: Appropriate for gestational age, RDS: Respiratory distress syndrome, hsPDA: Hemodynamically significant patent ductus arteriosus, MV: Mechanical ventilation, NIV: Non-invasive ventilation, IVH: Intraventricular hemorrhage, BPD: Bronchopulmonary dysplasia, ROP: Retinopathy of prematurity

Table 3. Neurodevelopmental assessment			
Variables	SGA n=65	AGA n=163	p
MDI, median IQR*	78 (56-92)	84 (76-96)	**0.01**
PDI, median IQR*	74 (55-87)	82 (73-94)	**<0.001**
Neurodevelopmental impairment, n (%)	25 (38.4)	32 (19.6)	**0.003**
MDI <70, n (%)	21 (32.3)	18 (11)	**<0.001**
PDI <70, n (%)	26 (40)	29 (17.7)	**<0.001**
Cerebral palsy, n (%)	6 (9.2)	4 (2.4)	**0.03**
Blindness, n (%)	2 (3)	1 (0.6)	0.19
Deafness, n (%)	0 (0)	1 (0.6)	1.00

*Non-parametric test
p<0.05 was considered significant (in bold)
SGA: Small for gestational age, AGA: Appropriate for gestational age, MDI: Mental development index, PDI: Psychomotor development index

However, recent studies suggest that preterm SGA infants have severe respiratory problems that can be attributed to altered endogenous surfactant metabolism, underexpression of surfactant protein genes, inadequate response to exogenous surfactant, irreversible underdevelopment of the terminal airways and gas exchange units in the lungs (21-23). Similar to our findings, Nobile et al. (24) conducted a study of 515 preterm infants born at or before 30 weeks' gestation and found that preterm SGA infants received more surfactant than the AGA group and had a higher incidence of BPD. Literature data indicate that being SGA doubles the incidence of BPD. The incidence of BPD and rate of poor neurodevelopmental outcomes due to BPD observed in our study are consistent with the literature (24-27).

Fetal malnutrition in periods of critical cell development may cause permanent alterations in various organs, including the brain. A correlation between GW and cognitive function has been posited in the literature (17). There are also studies indicating that preterm SGA infants have lower Bayley scores (19). Preterm and term-born children with SGA had lower cognitive scores compared with those with AGA (28). In contrast, Latal-Hajnal et al. (20) showed that for very low BW infants, being born SGA was not correlated with unfavorable neurodevelopmental course. Preterm birth is a major perinatal risk factor for neurodevelopment and the literature highlights heterogeneity in developmental outcomes of preterm children (29). The main reasons for this heterogeneity in the literature are the use of different gestational weeks and different neurodevelopmental evaluation scales in studies. Neurodevelopmental outcomes of SGA with <32 gestational weeks as the lowest gestational week were examined (7,30). NDI has been reported to be approximately 10% in term SGA infants and approximately 17% in SGA infants at <32 weeks of gestation (7,28). However, there are insufficient data on the neurodevelopment of SGA infants <30 weeks of gestation, who are more susceptible to poor neurodevelopment (31). In this respect, in our study, NDI was 38.5% in SGA premature infants with a gestational week of <30 weeks. It was approximately two times higher in SGA premature infants than AGA premature infants. Although it is not the right approach to attribute a poor NDI to a single cause, we have shown that being SGA is as significant a risk as any other morbidities.

According to our results, the cause of poor neurodevelopmental outcome in SGA premature infants may be the development of hypoxic brain injury due to recurrent episodes of hypoxia, hypercapnia, and respiratory acidosis due to high rates of respiratory morbidities. In addition, respiratory morbidities may have increased postnatal steroid use and contributed negatively to neurodevelopment. Therefore, being both premature and SGA may increase the risk of brain damage more than AGA infants (32). In addition, fluctuations in cerebral blood flow during hypoxic episodes can increase the risk of IVH and subsequently negatively affect neurodevelopmental outcomes. In a study evaluating preterm infants weighting less than 1000 g at birth when they reached 55 months of age, the risk of developmental sequelae was found to be 39%, and was associated with IVH grade and PVL (33). In another study, CP was reported in all preterm infants with stage III and stage IV IVH (34). CP, poor motor development, and significant sensory deficits were reported in another study of preterm infants with severe IVH (35). Consistent with the literature, we detected a significant correlation between IVH and neurodevelopmental sequela, and our logistic regression analysis showed that stage III and stage IV IVH were independent risk factors for neurodevelopmental impairment. We believe that

Table 4. Independent risk factors for neurodevelopmental delay			
	Relative risk	95% CI	p
Grade III-IV Intraventricular hemorrhage	9.85	2.37-40.96	**0.002**
Gestational age, <28 weeks	2.32	1.11-4.85	**0.02**
Small for gestational age	2.27	1.08-4.76	**0.02**
Postnatal corticosteroid treatment	2.62	1.07-6.41	**0.03**
Antenatal corticosteroid treatment	0.40	0.19-0.83	**0.01**
p<0.05 was considered significant (in bold) CI: Confidence interval			

IVH, PVL and postnatal steroid use reduce MDI and NDI while increase CP rate. It is an essential factor for poor neurodevelopmental outcome in out-of-hospital care, especially in family care after discharge. It is an essential factor that we could not evaluate in our study (30).

According to the few studies conducted in preterm SGA infants and our results, as the gestational week decreases, the risk of SGA-related poor neurodevelopmental outcomes exponentially increases compared to term SGA infants. However, it is not clear how much of an increased neurodevelopmental impairment risk for premature SGA infants has at which GA (28). A small head circumference at birth is a predictor of poor neurodevelopment at seven months and seven years old, according to another research. Rapid myelination and brain growth take place in the third trimester of human pregnancy. It is theoretically conceivable that SGA children might have slower brain development and an increased risk of neurodevelopmental issues in the future (36). Small head size at birth is associated with neurodevelopment. This may be the reason for our neurodevelopment delay in preterms with SGA. We believe that our results will make an essential contribution to the literature in this regard.

Räikkönen et al. (37) presented a study in which live births (8138 were born preterm) in Finland from 2006-2017, any mental or behavioral disorders were more frequent in the children exposed to antenatal corticosteroids. Our findings suggest a need for caution in administering antenatal corticosteroids. Similar to the literature, although we found antenatal steroids risk factors for the neurodevelopmental delay, prospective studies are required to make such a definitive judgment.

Study Limitations

The present study has certain limitations. A limitation of our study is that it was retrospective and single-centered. Other limitations are that the patients had no follow-up and neurodevelopmental evaluation until a later stage, and our data are based on the BSID-II because this was the scale used during the study period. Another limitation related to the retrospective data collection is that we were not able to use the most recently introduced 3rd edition of the Bayley Scales of Infant and Toddler Development (Bayley III). In light

of these, the MDI and PDI values of our patients may be lower compared to the current assessment scales (38). However, because risky pregnancies are referred to our center for follow-up, we were able to follow and include a large number of preterm infants in the sample group during the 2-year study period. A strength of this study is the standardization of neurodevelopmental outcome assessment provided by the patients' single-center follow-up and the institution-wide implementation of approaches consistent with those indicated in the current guidelines for neonatal morbidities. We also believe that our results provide important information about neurodevelopmental outcomes in SGA infants <30 weeks of gestation.

Conclusion

In conclusion, being SGA is a risk factor for neurodevelopmental delay. Especially at <30 weeks of gestation, the risk of poor neurodevelopmental outcome is higher than in term SGA infants. Strategies are needed to reduce the risk of neurodevelopmental impairment in preterm SGA infants.

Ethics

Ethics Committee Approval: Ethical approval was received for this study from the Local Ethics Committee of Dr. Zekai Tahir Burak Women's Health Training and Research Hospital (date: 29.05.2018, number:24/2018).

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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