Does Being Born Small For Gestational Age Affect Cerebellar Size In Neonates?

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Abstract

Objective: To investigate how cerebellar vermis height (CVH) and transverse cerebellar diameter (TCD) measurements are affected in SGA neonates.

Methods: A total of 176 [88 SGA and 88 appropriate for gestational age (AGA)] neonates between 26-42 weeks of gestation were included. Midsagittal plane through the anterior fontanel and coronal plane through the left mastoid fontanel were used to measure CVH and TCD, respectively. Cerebellar vermis height and TCD values were considered normal when they were $\geq 10^{\text{th}}$ percentile, according to nomograms of AGA neonates.

Results: Thirty-six asymmetric SGA neonates, 52 symmetric SGA neonates and their 88 gestational age-matched AGA controls were

studied. The percentages of neonates with normal CVH and TCD in the symmetric SGA subgroup were significantly lower than those in the AGA and asymmetric SGA subgroups. The percentages with normal CVH and TCD in the asymmetric SGA subgroup were also found to be low when compared with the AGA subgroup.

Conclusion: Growth and development of cerebellum may be less spared in SGA neonates. Further studies with larger series are needed in order to evaluate how being born SGA (symmetric and asymmetric) affects cerebellar size and also to see how these findings influence the neurocognitive outcomes of these infants at long-term follow-up.

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Title Page

Title: Does Being Born Small For Gestational Age Affect Cerebellar Size In Neonates?

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Short title: cerebellar size in small for gestational age

Key words: cerebellum, small for gestational age, brain sparing.

ABSTRACT

Objective: To investigate how cerebellar vermis height (CVH) and transverse cerebellar diameter (TCD) measurements are affected in SGA neonates.

Methods: A total of 176 [88 SGA and 88 appropriate for gestational age (AGA)] neonates between 26-42 weeks of gestation were included. Midsagittal plane through the anterior fontanel and coronal plane through the left mastoid fontanel were used to measure CVH and TCD, respectively. Cerebellar vermis height and TCD values were considered normal when they were $\geq 10^{\text{th}}$ percentile, according to nomograms of AGA neonates.

Results: Thirty-six asymmetric SGA neonates, 52 symmetric SGA neonates and their 88 gestational age-matched AGA controls were studied. The percentages of neonates with normal CVH and TCD in the symmetric SGA subgroup were significantly lower than those in the AGA and asymmetric SGA subgroups. The percentages with normal CVH and TCD in the asymmetric SGA subgroup were also found to be low when compared with the AGA subgroup.

Conclusion: Growth and development of cerebellum may be less spared in SGA neonates.

Further studies with larger series are needed in order to evaluate how being born SGA (symmetric and asymmetric) affects cerebellar size and also to see how these findings influence the neurocognitive outcomes of these infants at long-term follow-up.

INTRODUCTION

In small for gestational age (SGA) neonates, a suboptimal intrauterine environment leads to underdevelopment of the body and the brain [1,2].

In symmetric SGA, decreased head circumference (HC) accompanies decreased length and weight, whereas in asymmetric SGA, HC is spared and is normal for age [3]. It has been suggested that the brain may be relatively spared compared to other organs in asymmetric SGA neonates [4]. It is known that SGA neonates have a higher rate of abnormal neurodevelopment [5,6]. Moreover, disrupted cerebellar development is also associated with significantly poorer scores in the subtests for both neuromotor and mental development [7]. The biometric parameters used most frequently during cranial ultrasonography in neonates to evaluate cerebellar size and morphology include cerebellar vermis height (CVH) and transverse cerebellar diameter (TCD). In a study evaluating TCD by ultrasonography in appropriate for gestational age (AGA) and SGA neonates, Makhoul et al. emphasized 'cerebellar sparing effect' in asymmetric SGA neonates [8]. However, in animal studies of asymmetric intrauterine growth restriction (IUGR), reduced cerebellar growth was shown, despite the so-called 'brain sparing effect' [9-11]. In this study, our aim was to investigate how CVH and TCD measurements are affected in SGA neonates.

SUBJECTS and METHODS

In this study, we included a total of 176 (88 SGA and 88 AGA) neonates between 26-42 weeks of gestation born at Zeynep Kamil Maternity and Children's Training and Research Hospital, Istanbul, Turkey, between July 1, 2013 and June 30, 2014.

Large for gestational age neonates, those with congenital malformations, anomaly of central nervous system, chromosomal anomaly, evidence of congenital infection/meningitis, metabolic disease, cerebellar/intracranial hemorrhage and neonates who were one of a multiple birth were excluded.

Gestational age was calculated from the beginning of the last menstrual period of the mother and verified using early first trimester ultrasonographic data. Neonates with uncertain gestational age were also excluded.

Written informed consent was obtained from the parents and the local ethics committee approved the study protocol.

Neonates were weighed naked with an electronic scale (Sartorius AG, Germany) accurate to ± 5 g. Cases with birth weight less than 10th percentile and between 10th and 90th percentile for gestational age, according to Turkish growth charts, were classified as SGA and AGA, respectively [12]. Head circumference was measured with the same tape measure by the same investigator. Small for gestational age neonates were further classified according to their HC as asymmetric SGA (36 with $HC \geq 10^{th}$ percentile) and symmetric SGA (52 with $HC < 10^{th}$ percentile) [12]. Since 3rd percentile reference values for HC at birth were not available for our population, we did not separately categorize the neonates with subnormal HC (3rd-10th percentile). Symmetrically growth-restricted neonates may have suffered a genetic, infectious or

teratogenic insult early in utero. However, the majority of them were healthy, normal infants. They were at the lower end of the normal distribution of birth weights due to ethnic or constitutional reasons [13]. In this study, we included the symmetric SGA neonates with ethnic / constitutional factors. For each SGA infant, successively born, gestational age-matched AGA infant was included in the study. All AGA neonates had normal HC ($\geq 10^{\text{th}}$ percentile).

Cranial ultrasonography

All of the neonates underwent cranial ultrasonography within 24 hours of birth by one experienced neonatologist (EYI). A multifrequency 5-12 MHz sector probe (Philips En Visor C, Amsterdam, The Netherlands) was used in each case. The investigator was blinded to all subgroups. Midsagittal plane through the anterior fontanel and coronal plane through the left mastoid fontanel just behind the helix of the ear were used to measure CVH and TCD, respectively [14]. The optimal 2D image was frozen on the ultrasound screen, and afterwards the measurement was taken. Three repeated measurements of the CVH and TCD were performed in each neonate. For the repeated measurements, the image was unfrozen, the probe was reapplied to the neonate's head, the optimal image was obtained again and another measurement was taken. The mean value for the three repeated measurements was used for analysis.

Statistical analysis

Statistical analyses were performed using the IBM SPSS Statistics software (SPSS, Chicago, Illinois). The variables were investigated using visual histograms, probability plots and Shapiro-Wilk's test to determine whether or not they were normally distributed. Descriptive analyses were presented using means and standard deviations as the variables were normally distributed and the Student's t test was used to compare. Cerebellar vermis height and TCD values were

considered normal when they were $\geq 10^{\text{th}}$ percentile, according to nomograms of AGA neonates [14]. Chi-square test was used in order to compare the percentages of neonates with normal CVH and TCD in each subgroup. Pearson correlation coefficients were used to evaluate the correlations between the variables. A p value of less than 0.05 was considered statistically significant.

Accuracy for each cerebellar measurement was tested using intraclass correlation coefficient (ICC) with the strength of agreement scale described by Brennan and Silman [15]. Accuracy was considered very good for ICC above 0.80 and good for ICC between 0.61 and 0.80.

Interobserver reliability was evaluated by repetition of the cerebellar measurements by a neonatologist experienced in cranial ultrasound (SS) and blinded to previous measurements in a sub-sample of 20% of the main sample. These measurements and the originals were compared using ICC.

Intraobserver reliability was evaluated by repetition of the cerebellar measurements by the main author blinded to previous measurements in 20% of neonates from the main sample. These pairs of measurements were compared using ICC.

RESULTS

Thirty-six asymmetric SGA neonates, 52 symmetric SGA neonates and their 88 gestational age-matched AGA controls were studied. All attempts at obtaining both CVH and TCD were successful.

Gestational ages of SGA and AGA neonates were similarly distributed (36.4 ± 3.8 and 36.3 ± 3.8 wk, respectively). Mean birth weight was 1926 ± 723 vs 2699 ± 854 g ($p=0.001$) in SGA and AGA neonates, respectively. Mean HC (30.2 ± 3.1 vs 32.4 ± 2.7 cm, $p=0.001$), CVH (1.96 ± 0.2 vs 2.12 ± 0.2 cm, $p=0.001$) and TCD (4.62 ± 0.7 vs 4.9 ± 0.6 cm, $p=0.012$) values were found to be significantly lower in SGA neonates when compared with AGA neonates.

Demographic characteristics of the study group were presented in Table 1. The percentages of neonates with normal CVH and TCD ($\geq 10^{\text{th}}$ percentile) in the symmetric SGA subgroup were significantly lower than those in the AGA and asymmetric SGA subgroups. The percentages with normal CVH and TCD in the asymmetric SGA subgroup were also found to be low when

compared with the AGA subgroup (Table 2). Scatterplots showing the relationship between cerebellar dimensions and gestational age in AGA and SGA neonates were presented in Figure 1.

Furthermore, HC, CVH and TCD were all found to be positively correlated with gestational age in the AGA ($r=0.92$, $p<0.001$; $r=0.69$, $p<0.001$; $r=0.9$, $p<0.001$), asymmetric SGA ($r=0.95$, $p<0.001$; $r=0.74$, $p<0.001$; $r=0.9$, $p<0.001$) and symmetric SGA ($r=0.92$, $p<0.001$; $r=0.65$, $p<0.001$; $r=0.87$, $p<0.001$) subgroups, respectively.

Interobserver reliability was very good for CVH and TCD, with ICCs of 0.85 and 0.89, respectively. Intraobserver reliability was also very good for CVH and TCD, with ICCs of 0.93 and 0.91, respectively.

DISCUSSION

In this study, CVH and TCD measurements in SGA neonates were found to be significantly lower when compared with those in AGA neonates. Zuccotti et al., however, constructed a nomogram of CVH in SGA neonates and did not find any difference in CVH measurements between AGA and SGA neonates [16]. Huang and Liu demonstrated growth retardation in cerebellar vermis (decreased vermis superior-inferior distance and central vermian area) in SGA neonates only at late gestation [17]. However, the authors did not evaluate TCD. We preferred to measure both CVH and TCD in order to have a complete evaluation of cerebellar size and morphology.

Hill et al. evaluated TCD in 44 SGA fetuses and found normal values ($\geq 10^{\text{th}}$ percentile) in only 40.9% [18]. The investigators did not group their cases into asymmetric and symmetric SGA. Makhoul et al. sonographically measured TCD in AGA and SGA neonates and divided SGA neonates into two groups, asymmetric and symmetric SGA, according to their HC using the 3rd percentile as a cut-off [8]. They reported that TCD was preserved in the majority of the asymmetric SGA neonates (85.7%, not statistically different from that observed in AGA neonates) and less preserved in symmetric SGA neonates born after severe IUGR (60.7%, statistically significant when compared to AGA neonates). Snijders et al. reported that in IUGR, cerebellar size is reduced in proportion to severity of the disease [19].

To our knowledge, this is the first study in the literature that evaluates cerebellar size with both CVH and TCD measurements in symmetric and asymmetric SGA neonates. In this study, percentages of neonates with normal CVH and TCD ($\geq 10^{\text{th}}$ percentile) were found to be significantly lower in the symmetric SGA subgroup (40.4%, 44.2%) than in the asymmetric SGA (83.3%, 77.8%) and AGA (97.7%, 92%) subgroups. Moreover, the percentages with normal CVH and TCD in the asymmetric SGA subgroup were also found to be significantly lower than the AGA subgroup. The differences in results between this study and that of Makhoul et al. could, in part, be due to different cut-off percentiles used for defining SGA status [8]. There are animal studies evaluating the effects of IUGR on brain development [9,10]. The degree of fetal hypoxemia in these studies was similar to that seen in human growth restricted fetuses. It is speculated that, although there was a brain sparing effect in hypoxemic fetuses, such that there was no reduction in brain weight compared to controls, several aspects of brain development, in particular the growth of cerebellum and myelination of cortical white matter, were affected. Following chronic hypoxemia during late gestation in fetal sheep, which induces asymmetric

growth restriction, there is reduced growth of cerebellum [10]. The findings of these animal studies are compatible with our results such that we also found significantly low percentages of normal CVH and TCD in asymmetric SGA neonates as well as symmetric ones. The so-called ‘cerebellar sparing effect’ may be less pronounced in asymmetric SGA neonates in contrast to the findings of Makhoul et al. Therefore, during clinical practice, CVH and TCD measurements should be interpreted with caution in an SGA neonate.

It could be more appropriate to categorize the SGA neonates in this study as asymmetric or symmetric based not only on a single HC parameter but also on ponderal index [13]. Vik et al. used ponderal index (below the 10th percentile as asymmetric, at the 10th percentile or above as symmetric SGA) as a cut-off between asymmetric and symmetric SGA neonates [20]. Since ponderal index percentile values at birth were not available for our population, we could not use ponderal index for discrimination between asymmetric and symmetric growth restriction. This is a limitation of our study. An additional limitation of this study is that the subgroup of asymmetric SGA is quite small. Therefore, studies with larger subgroups are needed in order to obtain more accurate results.

In another study by Makhoul et al., frontal lobe dimensions in normal and growth-restricted neonates were sonographically evaluated, and these dimensions were found to be significantly low in SGA neonates [21]. In addition to decelerating fetal weight, the demonstrated decelerations in frontal lobe and cerebellar growth may be of help for perinatologists and neonatologists when deciding on the optimal timing of delivery of a fetus with severe IUGR. After all, these decelerations in the growth of brain parts during severe IUGR might impair future neurodevelopment in these infants. Graça et al. found significantly low CVH, but not TCD, in preterm SGA infants at term-equivalent age [22]. There are MRI studies reporting that

infants who have a smaller cerebellum at term-equivalent age may be at increased risk of neurodevelopmental problems [23-25]. Unfortunately, we did not perform neurodevelopmental follow-up of these SGA neonates with normal and abnormal cerebellar growth. This is another limitation of our study.

In conclusion, growth and development of cerebellum may be less spared in SGA neonates. Further studies with larger series are needed in order to evaluate how being born SGA (symmetric and asymmetric) affects cerebellar size and also to see how these findings influence the neurocognitive outcomes of these infants at long-term follow-up.

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DECLARATION OF INTEREST

The authors report no declaration of interest.

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Figure Legends:

Figure 1. Scatterplots of cerebellar dimensions against gestational age: a) CVH (cm) and b) TCD (cm). AGA neonates are represented by circles and SGA neonates are represented by squares. Mean fit lines are represented by continuous lines for AGA neonates and by dotted lines for SGA neonates.

Table 1. Demographic characteristics of the study population.

subgroups SGA	AGA	asymmetric SGA	symmetric
n	88	36	52
HC percentile	10 th -90 th	10 th -90 th	<10 th
Female:male *	50:38	15:21	36:16
Gestational age (wk)(%)			
<32	13.6	8.3	15.3
32-36	35.2	19.4	46.1
>36	51.1	72.2	38.4
Birthweight (g)(%)			
<1000	1.1	8.3	13.4
1000-1499	10.2	5.5	28.8
1500-2500	28.4	36.1	48
>2500	60.2	50	9.6

*no statistical significance in terms of gender. AGA: appropriate for gestational age, SGA: small for gestational age, HC: head circumference.

Table 2. Percentages with normal¹ CVH and TCD in study subgroups.

subgroups symmetric SGA	AGA	asymmetric SGA	
n	88	36	52
% with CVH $\geq 10^{\text{th}}$ p 40.4% ⁴	97.7%	83.3% ²	
% with TCD $\geq 10^{\text{th}}$ p 44.2% ⁵	92%	77.8% ³	

CVH: cerebellar vermis height, TCD: transverse cerebellar diameter, AGA: appropriate for gestational age, SGA: small for gestational age.

¹normal: CVH and TCD $\geq 10^{\text{th}}$ percentile according to nomograms of AGA neonates.

²p:0.007 when compared with percentage in AGA neonates, p<0.001 when compared with percentage in symmetric SGA.

³p:0.036 when compared with percentage in AGA neonates, p:0.002 when compared with percentage in symmetric SGA.

⁴p<0.001 when compared with percentage in AGA neonates.

⁵p<0.001 when compared with percentage in AGA neonates.