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Original Article

Comparison of bone age in small-for-gestational-age children vs appropriate-for-getational-age children

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Abstract

Background About 10-15% small-for-gestational-age children are in higher risk for having linear growth retardation due to growth hormone-insulin like growth factor 1 axis defect (GH-IGF 1) which causes bone age delay.

Objectives To compare bone age in 24-36 month old children born small-for-gestational-age (SGA) to that in children born appropriate-for-gestational-age (AGA).

Methods A cross-sectional study was conducted in Hasan Sadikin General Hospital, Bandung, from January to April 2009. Subjects consisted of 50 healthy children of 24-36 months old (25 children born at term, SGA, 25 children born at term, AGA). We compared the appropriateness and delay of bone age between the two groups.

Results Mean bone age in the SGA group was 20.8 (SD 7.7) months, and in the AGA group was 25.7 (SD 7.1) months (P=0.022). Mean bone age deficit was -10.5 (6.5) months in the SGA group and -5.5 (SD 5.7) months in the AGA group (P=0.009). The prevalence ratio was 1.77 (95% CI: 1.19–2.62). Bone age delay was found to be higher in children born SGA than that in children of the other group (23 vs 13). On the contrary, appropriate bone age was found more in children born AGA (12 vs 2) (P=0.002).

Conclusion Bone age delay in 24-36 months old children born small-for-gestational-age was found to be higher than in those born appropriate-for-gestational-age. **[Paediatr Indones. 2010;50:73-9]**.

Keywords: *Small-for-gestational-age, appropriate-for-gestational-age, bone age, growth retardation*

Small-for-gestational age (SGA) refers to babies who have birth weight and/or birth length less than 10th percentile according to Lubchenco gestational age curve.[1-3] According to present data, there were about 2.3-10% of SGA babies.[4] Ministry of Health of Indonesia stated that in 2004 there were 7.6% babies born as SGA in Indonesia.[5] SGA babies will have intrauterine growth retardation, which impacts GH-IGF axis (growth hormone-insulin like growth factor) that delays bone maturity. Resulting in growth spurt impairment in their childhood related to short stature.[6,7]

Most SGA children will do their growth catch up and get their final height >-2 SD; this process starts in the first year of life and will be completed in 2 years of age.[8-11] About 10-15% of SGA children will have their height <-2 SD.[12,13] Study by Hediger et al[4] found that SGA children will have -0.06 height deficit at 3-4 years old. Short stature children born SGA who do not catch their growth spurt at 2-3 years old have to be managed by a pediatric endocrinologist.[2]

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The relationship between the etiology of intrauterine growth retardation and postnatal growth pattern is still unexplainable, but it is thought to be due to defect in GH-IGF-1 axis. This is supported by evidence that early mechanism of growth spurt is hypersecretion of growth hormone (GH).[14] Studies show low GH secretion and insulin growth factor-1 (IGF-1) serum concentration in children with failure to catch up,[15-19] and GH replacement therapy in short stature children will accelerate growth spurt and significantly increase body height. The aim of this study was to determine and to compare bone age in children aged 24-36 months born SGA to that in children born AGA.

Methods

In this cross sectional study we included babies born at term, appropriate-for-gestational-age and those born small-for-gestational-age (AGA and SGA) in Hasan Sadikin General Hospital from January 01 to December 31, 2006. At the start of the study the babies were 24-36 months old. We excluded children with chronic disease (tuberculosis, hepatic cirrhosis, nephrotic syndrome, and malignancy), severe malnutrition, and major congenital anomaly. Parental informed consent was obtained from all subjects.

We estimated the number of required subjects by means of plot study; 23 subjects per group were needed. Bone age was measured using X-ray examinations of the left hand by two radiologists. The results were compared to standard presented in Greulich-Pyle atlas. Bone age's result was described in months and was considered appropriate if the results within $\pm$ 3 months.

To analyze parents' characteristics, nutritional status, and bone age ratio to chronologic age data, we used x^2 test. To analyze subjects' characteristics data we used t-test. The prevalence ratios were measured. Appropriateness of bone age results between two radiologists were tested using coefficient of agreement Kappa. To measure Kappa index (K), we used 2

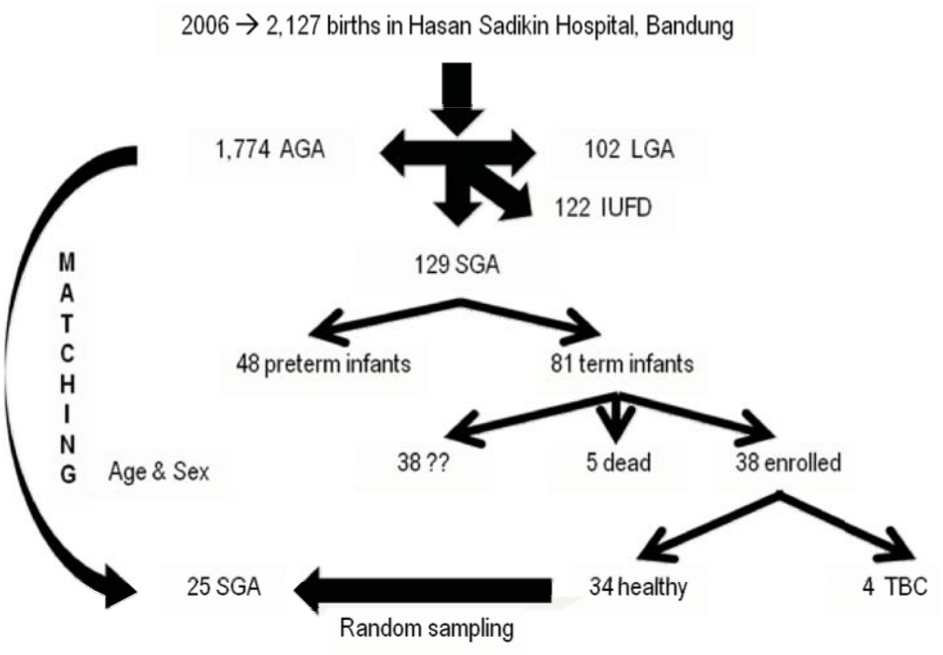

Figure 1. Ilustration of birth in Hasan Sadikin Hospital, Bandung, 2006 and methods to determine study subjects

SGA = small-for-gestational-age
AGA = appropriate-for-gestational-age
LGA = large-for-gestational-age
IUFD = intrauterine fetal death
TBC = tuberculosis

x^2 table. Comparison of bone age results by two radiologists was analyzed using Wilcoxon test and appropriateness of bone age results by two radiologists was analyzed using McNemar x^2 test. P value of <0.05 was considered statistically significant. We use SPSS version 15.0 for Windows 2007, SPSS inc, Chicago-Illinois, USA for all analyses.

This study had been approved by Ethical Committee of Medical Faculty of Padjadjaran University, Hasan Sadikin General Hospital, Bandung.

Results

There were 2127 babies born in Hasan Sadikin General Hospital from January to December 2006, consisted of 129 children born SGA 1774 children born AGA, and 122 cases of intrauterine fetal death (IUFD). From the 129 SGA children, there were 81 children born as term and 48 as preterm babies. Out of 81 children born SGA, 5 of them died, 38 were enrolled, and 38 children could not be traced. From the 38 enrolled children, there were four children excluded because of tuberculosis disease, so in the beginning we had 34 children enrolled to the study, and 25 of them were randomly selected (11 boys, 14 girls). Term AGA children were selected as the control group with well-matched age and sex.

General characteristics of the subjects included sex, birth weight, birth length, gestational age, chronological age, body weight, body height, nutritional status, parent's educational level, and family income (**Table 1**).

Birth weight and birth length of the SGA group were smaller compared to those of the AGA group, and statistically significant ($P<0.001$). Mean body weight of the AGA group was 11.9 (1.5) kg compared to the SGA group 11.04 (1.23) kg, and also statistically significant. There were more severely stunted children in the SGA group compared to the AGA group (20% vs. 4%) but the nutritional status was not statistically significant according to the weight/height, height/age curve, and weight/age. There were no significant statistically differences between father's and mother's educational level, and family income [data not shown].

In **Table 2**, we can see that both radiologists' results were not significantly different for either SGA or AGA group.

Table 3 shows that bone age measurement between two radiologists consisted of 43 well-matched results (nine were appropriate and 34 were delayed) and seven ill-matched results (two cases determined as delayed by A, but as appropriate ones by U; and five case determined as appropriate bone age by A, but as delayed bone age by U). A kappa index was

Table 1. General characteristics

Subjects' characteristics	SGA n = 25	AGA n = 25
Sex		
Birth weight, mean (SD) g	11/14	11/14
Birth length, mean (SD) cm	2,209 (248)	3,119 (304)
Weight, mean (SD) kg	46.0 (2.6)	49.1 (1.4)
Height, mean (SD) cm	11.04 1.23)	11.9 (1.5)
Nutritional status	84.3 (4.6)	86.3 (4.9)
W/H		
Overweight	0	1
Median	16	19
Wasted	9	5
H/A		
Median	13	13
Stunted	7	6
Severely stunted	5	1
W/A		
Median	17	20
Underweight	8	5

Note: # = t-test; * = x^2 test; SD =standard deviation; W=weight; H=height; A=age

Table 2. Comparison of bone age measurement in 24-36 month old children born SGA and AGA between two radiologists (n=50)

Variable	Radiologist A	Radiologist U	Significance
Bone age, mean (SD) mo	23.24 (7.76)	22.74 (7.80)	Zw = 0.675 P = 0.50
Median	24	18	
Interval	3-36	6-36	
Deficit, mean (SD) mo	-8.02 (6.56)	-8.50 (6.46)	Zw = 0.638 P = 0.524
Median	-9	-9	
Interval	-27 s/d 4	-19 s/d 5	

Note: Z_w = Wilcoxon test

Table 3. Agreement of the bone age result of 24-36 months old children born SGA and AGA between two radiologists

Bone Age		U Delay	U Appropriate	N
A	Delay	34	2	36
	Appropriate	5	9	14
Number		39	11	50

Note: x^2 McNemar; *P* = 0.453; Kappa Index = 0.628

0.628 which meant well matched (Fleiss) or substantial (Landis and Koch).

Radiologic bone age measurement of the subjects was compared to Greulich and Pyle atlas. In **Table 4**, we see significant differences between means of bone age of SGA and AGA. Significant differences were also found in means of bone age deficit compared to chronological age between the SGA and AGA.

Table 5 shows that in the SGA group there were 23 (92%) children with delayed bone age compared to 13 (52%) children in the AGA group. In the SGA group, there were only two children with appropriate bone age compared to 12 children in the AGA group. Comparison of bone age in 24-36 months old children between those born SGA and those of AGA group was statistically significant (P=.002).

Table 4. Comparison of bone age and bone age deficit between two groups

Results	Group		P value
	SGA n = 25	AGA n = 25	
Chronological age, mean (SD) mo	31.0 (3.8)	31.0 (3.8)	.732#
Bone age, mean (SD) mo	20.8 (7.7)	25.7 (7.1)	.022*
Bone age deficit, mean (SD) mo	-10.5 (6.5)	-5.5 (5.7)	.009*

Note: # = t-test; * = Mann-Whitney test; SD = standard deviation

Table 5. Comparison of bone age in 24-36 months old SGA and AGA children

Delay/ Appropriate	Group		P value*
	SGA n = 25	AGA n = 25	
Delay	23	13	0.002
Appropriate	2	12	

Note: * = x^2; Prevalence ratio = 1.77 (95% CI:1.19–2.62)

Discussion

The incidence of newborn with SGA in our study (129/2127) was quite similar to previous data that there were 2.3-10% babies born SGA;[4] the overall incidence of SGA in Indonesia is 7.6%.[5] The mean birth weight and length of the SGA group were smaller compared to those of the AGA group. Mean birth weight of the SGA group was 2209 (SD 248) gram and it was statistically significant smaller compared to the AGA group 3119 (SD 304) gram (P<0.001). Mean body length of the SGA group was also statistically significant shorter compared to the AGA group. There was no statistical differences in the gestational age between SGA and AGA group. These data show that children born AGA have heavier birth weight and longer birth length compared to SGA children. SGA was defined as children who were born with birth weight/birth length less than 10th percentile according to the population data for identical gestational age according to the Lubchenco curve.[1-3,20-23]

The mean chronologic age in the SGA and AGA group were not significantly different. There was different mean body height of the SGA group compared to the AGA group. This was similar to the results of the study conducted by Hediger et al.[4,24] But with different interval. Study of Strauss and Dietz[25] showed a -0.50 deficit at the age of 7 years. From the previous studies, we can see that the older the children, the bigger the height deficit in the SGA group compared to the AGA group, which finally resulted in short stature.

In the SGA group there were five children with height/age <-2 SD (severely stunted) compared to the AGA group; one child. Babies born SGA are in higher risk for having growth retardation (short stature).[26,27] In this study we found 5-10% higher incidence compared to the study done by Karlberg et al[12] dan Leger et al[13] which found that about 10-15% of SGA children will have their height <-2 SD. Nutritional status examinations showed no statistical differences, either using the weight/height, height/age, or weight/age.

Bone age were examined by two radiologists using standardized Greulich and Pyle atlas.[26,28,29] The results of the examinations between the two radiologists were tested using the coefficient agreement Kappa. The Kappa index was 0.68, and it was not statistically different (P=.453) which means that the two radiologists were well-matched (according to Fleiss) or substantial (according to Landis and Koch).[30] Comparison between both radiologists showed no significant differences on bone age variable (*P*=0.50) as well as on bone age deficit variable (*P*=0.52). The bone age examinations showed a reliable and consistent data.

This study showed that comparison of bone age delay in 24-36 month old children born SGA and AGA was similar to previous prediction. Bone age of the SGA and AGA group showed significant statistical differences: there was more children with bone age delay in the SGA group compared to the AGA group.

Comparison between chronologic age and bone age of the SGA and AGA children showed significant difference. More children in the SGA group had delayed bone age compared to those in the AGA group (23 vs 13) and more children in the AGA group had appropriate bone age compared to those in the SGA group (12 vs 2). The PR was 1.77 (95% CI 1.19 to 2.62) which means that children in the SGA group have 1.77 times higher risk for having delayed bone age. SGA children will have delayed bone age due to GH-IGF 1 axis defect that will decrease GH-IGF 1 secretion level.[15-18,31-34]

Bone maturity is one of growth process and influenced by many factors such as genetics, hormonal, chronic diseases, nutrition, and social-economic status.[26,27] Confounding factors in this study were social-economic status (parents' educational level and family income), which showed no significant differences.

Genetic factor is one of the factors that influences bone maturity. Study of Arends et al[33] showed that SGA babies with 191 IGF-1 allele will be shorter than those without. Research by Abuzzahab et al[35] also showed a correlation between pre- and post natal growth restriction with gene IGF-1R mutation. In this research, they found insulin-like growth factor releasing factor (IGF-RF) gene mutation in SGA children that changes the arrange of Arg108Gln in one allele and Lys115Asn in other allele, with point mutation CGA–TGA (Arg59 stop) that decrease the amount of IGF-1 receptor.

Linear growth can be measured using the body height and bone age. There was no significant differences in body height measurement in 24-36 months old children, although there was height deficit -0.3 SD in the SGA group compared to the AGA group. Growth measurement using bone age is a better tool compared to body height measurement because body height measurement only describes actual mean time growth of the children, while bone age measurement can be used to determine growth status and to predict prognosis and final body height.[36]

There were several limitations of this study. First, we recruited the AGA and SGA subjects from medical record. Second, we did not classify SGA into symmetric and asymmetric, so we could not determine which SGA group that has higher risk for having bone age delay. In this study, we could only conclude that SGA children have 1.77 times higher risk for having bone age delay compared to the AGA children. Third, we did not measure the GH and IGF-1 level of the subjects. We suggest further research on bone age delay that also classified the SGA group including GH and IGF-1 level measurement.

We concluded that there is bone age delay in 24-36 months old children more in those born SGA compared to those born AGA.

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