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Original Article

Bone age in prepubertal children with nonfamilial or familial idiopathic short stature and prepubertal short-stature children born small for gestational age: a longitudinal data analysis

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Abstract. This retrospective study aimed to clarify the characteristics of bone maturation using longitudinal data in short-stature prepubertal children. Children with chronological ages (CAs) of 4.5–10.5 yr with nonfamilial idiopathic short stature (ISS, n = 95), familial ISS (FSS, n = 21), and short-stature children born small for gestational age (SGA, n = 23) were selected, of which 435 left-hand plain radiographic images were evaluated. Bone age (BA) delay was defined as BA minus CA. In the ISS group, there was a statistically significant difference in median BA delay among the CA groups ($P < 0.001$), as median BA delay gradually increased from 5- to 9-yr-old groups (−1.06 [range, −2.17 to 0.27] and −2.45 [range, −4.35 to −0.32] yr, respectively). In the FSS group, median BA delays were approximately −1 yr in all CA groups. In the SGA group, median BA delay gradually decreased from 7- to 10-yr-old groups (−1.96 [range, −2.99 to 0.56] and −0.04 [range, −2.44 to 0.92] yr, respectively), but with no significant difference ($P = 0.647$). The heavier weight of children with FSS and the probable earlier onset of adrenarche in children born SGA compared to those with ISS could have affected bone maturation.

Key words: bone age, skeletal maturity, idiopathic short stature, familial short stature, small for gestational age

Introduction

Bone age (BA), an important indicator of growth and maturity, is used in diagnosis, policy decision-making, and prediction of adult height. Factors promoting bone maturation include GH, thyroid hormone, and sex hormones. Prepubertal BA is delayed compared to chronological age (CA) not only in untreated GH-deficient children but also in children with non-familial idiopathic short stature (ISS) or short stature and were born small for gestational age (SGA).

Through analyzing cross-sectional data, degrees of BA delay compared with CA are approximately 1.5–2.0 yr at children aged 8–11 yr with nonfamilial ISS, and 1.0–2.0 yr until 8 yr of age in children born SGA (1). It is unclear why BA is delayed in prepubertal children without endocrine abnormalities. In contrast, BA accelerates in prepubertal obese children (2–5), and the timing of adrenarche affects bone maturation in prepubertal children with normal stature (6, 7).

This study aimed to clarify the characteristics and associated factors of bone maturation in prepubertal children with nonfamilial or familial ISS and prepubertal short-stature children born SGA by analyzing longitudinal data. To my knowledge, this is the first report to evaluate BA in relation to CA using longitudinal data in short-stature children without endocrine abnormalities.

Methods

Study participants

Study participants comprised of children with nonfamilial or familial ISS, or short-stature children born SGA who had visited the Department of Pediatrics in the Toho University Omori Medical Center between December 2004 and November 2020. The exclusion criteria were as follows: (i) a height standard deviation (SD) score at the first visit of ≥ −2, (ii) puberty before the first visit, and (iii) a history of growth-affecting medications.

Children with ISS were defined as having normal birth size and body proportions, and no evidence of systemic, endocrine, nutritional, or chromosomal abnormalities (8). ISS was further classified as either

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nonfamilial or familial. Children with familial ISS were defined as those with any parental height score of < −2 SD, or whose target height score was < −1.5 SD. Hereafter, nonfamilial and familial ISS are referred to as ISS and familial short stature (FSS), respectively. Children born SGA were defined as those with a birth height and weight < 10th-percentile values for gestational age. Children who had both FSS and SGA were excluded.

Study design

In this retrospective study, one investigator evaluated the bone ages in left-hand plain radiographic images using the Tanner-Whitehouse 2 radius-ulna-short bones (RUS) method standardized for Japanese children (9). Bone ages were evaluated every 6 months to 1 yr. All prepubertal left-hand plain radiographs taken for each participant were included in the analysis. BA delay was defined as BA minus CA.

Each CA group consisted of children with the specified CA ± 0.5 yr, and 5- to 10-yr-old groups were analyzed. Radiographic images taken during CAs of < 4.5 yr were excluded because the younger BA in males < 3.2 yr and females < 3.3 yr cannot be evaluated using the Tanner-Whitehouse 2 RUS method standardized for Japanese children. Plain radiographic images taken during CAs of > 10.5 yr were also excluded because bone maturation slows down in children during adolescence, unless puberty has begun and sex hormone levels have increased.

Height SD score, weight SD score, percentage of overweight (POW), and body mass index (BMI) SD score were calculated using Excel-based Clinical Tools for Growth Evaluation of Children's Growth Charts (10, 11), based on 2000 national survey data of Japanese children (12, 13). POW is commonly used to evaluate obesity in Japan and is calculated using the following formula: (measured weight − standard weight) / standard weight × 100 (14), with normal values between −20% and +20% for school-age children. POW in children aged < 6 yr was calculated using the standard weight according to sex and height, and POW in children aged ≥ 6 yr was calculated using the standard weight according to sex, CA, and height. Height and weight ± SD scores at birth were calculated using the same growth charts, based on 2014 Japanese neonatal anthropometric charts for gestational age at birth (15). The target height was calculated using the method described by Ogata *et al*. (16). Puberty onset was defined as the time when the testicular volume was > 3 mL in males, or breast development was Tanner stage ≥ 2 in females.

The Mann-Whitney U test was used for statistical comparisons between two groups, and the Kruskal-Wallis H test was used for statistical comparisons among ≥ 3 groups, followed by Dunn's post hoc test. A Wilcoxon signed-rank test was used to compare the two related samples. Statistical significance was set at $P < 0.05$. Results are expressed as medians with ranges, unless otherwise specified. All statistical analyses were performed using StatMate V (ATMS Co., Ltd., Chiba, Japan).

This study was approved by the ethics committee of the Toho University Omori Medical Center (No. M20296). The requirement for informed consent was waived in view of the retrospective study design.

Results

The ISS, FSS, and SGA groups consisted of 95 (54 males; 290 left-hand plain radiographic images), 21 (10 males; 82 plain radiographic images), and 23 (8 males; 63 plain radiographic images) children, respectively. The clinical characteristics of the three groups are shown in **Table 1**. There was no significant difference in median gestational age, and initial median CA, height SD, and body weight SD scores among the three groups; however, the median birth height and weight SD scores were significantly lower in the SGA group than in the other two groups. The median paternal and maternal height SD scores and the target height SD score were significantly lower in the FSS group than in the other two groups. The initial median insulin-like growth factor-1 (IGF-1) SD score was significantly lower in the ISS group than in the SGA group.

The chronological median BA delay changes are shown in **Fig. 1**. In the ISS group, the median BA delays were approximately −1 to −2.5 yr in all CA groups, with a statistically significant difference ($P < 0.001$). The median BA delay gradually progressed from 5-yr-olds (−1.06 [−2.17 to 0.27] years) to 9-yr-olds (−2.45 [−4.35 to −0.32] yr), which showed the highest delay. The median BA delay among 8-yr-olds (−1.72 [−3.86 to −0.08] years) was significantly greater than that among 5- and 6-yr-olds (−1.17 [−2.91 to 0.87] years) ($P < 0.001$ and $P < 0.05$, respectively). The median BA delay among 9-yr-olds was significantly greater than that among 5-, 6-, and 7-yr-olds (−1.48 [−3.42 to 0.32] yr) ($P < 0.001$, $P < 0.001$, and $P < 0.01$, respectively). The median BA delay among 10-yr-olds (−2.22 [−4.61 to 0.61] yr) was significantly greater than that among 5- and 6-yr-old groups ($P < 0.001$ for both groups).

In the FSS group, median BA delays were approximately −1 yr in all the CA groups, with 8-yr-olds showing the highest median BA delay (−1.26 [−2.48 to −0.27] yr), but with no significant difference among the CA groups ($P = 0.383$).

In the SGA group, median BA delays were approximately −2.0 to 0 yr in all CA groups. The median BA delay gradually decreased from 7-yr-olds (−1.96 [−2.99 to 0.56] yr), which showed the greatest delay, to 10-yr-olds (−0.04 [−2.44 to 0.92] yr), but with no significant difference among the CA groups ($P = 0.647$).

There were statistically significant differences in median BA delays in the 7-, 8-, 9-, and 10-yr-old groups among the ISS, FSS, and SGA groups ($P < 0.01$, $P < 0.05$, $P < 0.001$, and $P < 0.01$, respectively). Median BA delays among 7- and 9-yr-old ISS groups were significantly

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Table 1. Comparisons of clinical characteristics among three groups

n (male/female)	ISS group 95 (54/41)	FSS group 21 (10/11)	SGA group 23 (8/15)	P value	Multiple comparison
At birth					
Gestational age (weeks)	39.3 (30.7 to 41.4)	39.0 (29.0 to 41.6)	39.3 (25.3 to 40.9)	0.487	
Body weight (g)	2,830 (1,566 to 3,582)	2,906 (1,353 to 3,352)	2,198 (518 to 2,838)	< 0.001	SGA < ISS, FSS
Body weight SDS	−0.51 (−2.22 to 1.78)	−0.23 (−1.92 to 1.06)	−2.09 (−4.39 to −1.00)	< 0.001	SGA < ISS, FSS
Height (cm)	48.0 (38.2 to 51.1)	47.0 (39.2 to 50.5)	43.5 (27.8 to 47.0)	< 0.001	SGA < ISS, FSS
Height SDS	−0.60 (−2.87 to 1.33)	−0.75 (−2.05 to 0.94)	−2.34 (−3.21 to −1.32)	< 0.001	SGA < ISS, FSS
Parent's height					
Father's height (cm)	169.0 (160.0 to 180.0)	162.0 (152.0 to 175.0)	170.0 (160.0 to 184.0)	< 0.001	FSS < ISS, SGA
Father's height SDS	−0.31 (−1.86 to 1.59)	−1.52 (−3.24 to 0.72)	−0.14 (−1.86 to 2.28)	< 0.001	FSS < ISS, SGA
Mother's height (cm)	155.0 (148.0 to 164.0)	147.0 (140.0 to 158.0)	153.0 (148.0 to 163.0)	< 0.001	FSS < ISS, SGA
Mother's height SDS	−0.58 (−1.91 to 1.11)	−2.09 (−3.42 to −0.02)	−0.96 (−1.91 to 0.92)	< 0.001	FSS < ISS, SGA
Target height SDS	−0.49 (−1.33 to 1.68)	−1.62 (−2.38 to −1.06)	−0.49 (−1.53 to 0.81)	< 0.001	FSS < ISS, SGA
At first visit					
Chronological age (years)	4.4 (0.8 to 10.4)	4.3 (0.8 to 9.6)	5.0 (1.6 to 10.2)	0.224	
Height SDS	−2.44 (−3.34 to −1.88)	−2.58 (−3.65 to −2.01)	−2.47 (−3.98 to −2.01)	0.390	
Body weight SDS	−1.88 (−3.80 to −0.15)	−1.75 (−3.43 to 0.29)	−2.10 (−0.72 to −4.26)	0.432	
IGF-1 SDS	−1.04 (−3.31 to 0.91)	−0.88 (0.31 to −1.89)	−0.39 (−2.40 to 1.64)	0.020	ISS < SGA

All data are expressed as medians (ranges). ISS, idiopathic short stature; FSS, familial short stature; SGA, small for gestational age; SDS, standard deviation score.

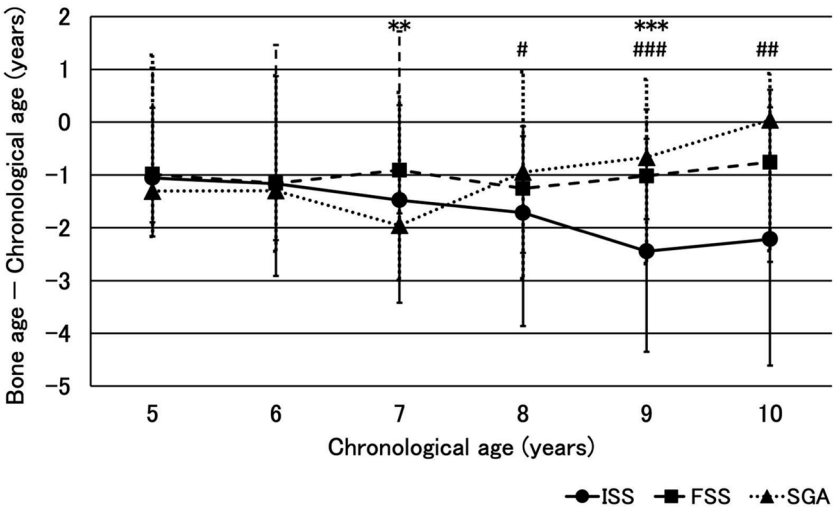

Fig. 1. Chronological changes in median (range) bone age delay in children with idiopathic short stature (ISS), familial short stature (FSS), and children born small for gestational age (SGA). There were statistically significant differences in median bone age delays in the 7-, 8-, 9-, and 10-yr-old groups among the ISS, FSS, and SGA groups. ** $P < 0.01$; *** $P < 0.001$ between ISS and FSS groups; # $P < 0.05$; ## $P < 0.01$; ### $P < 0.001$ between ISS and SGA groups.

greater than those in age-similar FSS groups, and median BA delays among 8-, 9-, and 10-yr-old ISS groups were significantly greater than those in age-similar SGA groups.

In the ISS group, sex-specific chronological changes in median BA delay were examined (168 plain radiographic images in 54 males, and 122 plain radiographic images in 41 females) (**Fig. 2**). There was no significant difference in median BA delay between males and females in each CA group, except in the 6-yr-old group.

Comparisons of the height and weight SD scores among the three groups are shown in **Table 2**. The median height SD scores among different CAs in the three groups were approximately −2.0 to −2.5, showing no significant differences. Median body weight SD scores in all CA groups were approximately −2.0, −1.5 to −2.0, and −1.5 to −3.0 in the ISS, FSS, and SGA groups, respectively. The median body weight SD scores among 6-, 7-, and 8-yr-olds in the FSS group were significantly higher than those in the SGA group ($P < 0.05$ for all groups).

Comparisons of the POW and BMI SD scores among the three groups are shown in **Table 3**. The median POWs among 6-, 7-, and 8-yr-olds in the FSS group were significantly higher than those in age-similar

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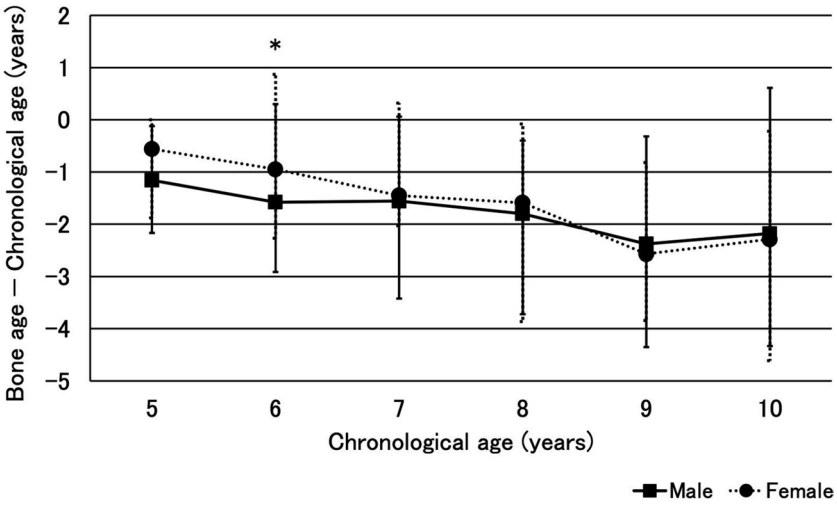

Fig. 2. Chronological changes in median (range) bone age delay in male and female children with idiopathic short stature. There was no significant difference in median bone age delay in each chronological age group between males and females, except in the 6-yr-old group.* $P < 0.05$.

Table 2. Comparisons of height and body weight SD scores among three groups

CA (years)	ISS group (n)		FSS group (n)		SGA group (n)		P value	Multiple comparison
Height SD score								
5	−2.24 (−3.18 to −0.99)	(36)	−2.61 (−3.04 to −1.88)	(11)	−2.01 (−2.50 to −1.63)	(8)	0.058	
6	−2.31 (−3.35 to −1.43)	(56)	−2.41 (−3.25 to −1.84)	(14)	−2.30 (−3.56 to −1.61)	(13)	0.281	
7	−2.37 (−3.35 to −1.58)	(51)	−2.55 (−3.25 to −1.84)	(19)	−2.16 (−3.50 to −1.77)	(7)	0.666	
8	−2.29 (−3.55 to −1.70)	(55)	−2.44 (−3.02 to −2.05)	(12)	−2.24 (−3.52 to −1.77)	(11)	0.630	
9	−2.27 (−3.48 to −1.64)	(46)	−2.54 (−2.91 to −2.04)	(18)	−2.31 (−3.50 to −1.69)	(14)	0.353	
10	−2.38 (−3.17 to −1.54)	(46)	−2.41 (−2.70 to −2.12)	(8)	−2.33 (−3.10 to −1.91)	(10)	0.074	
Body weight SD score								
5	−1.76 (−3.40 to 0.15)	(36)	−1.72 (−2.06 to 0.13)	(11)	−1.57 (−3.48 to −0.81)	(8)	0.144	
6	−1.93 (−4.07 to 0.09)	(56)	−1.55 (−2.93 to 0.33)	(14)	−2.63 (−5.19 to −0.90)	(13)	0.023	SGA < FSS
7	−1.94 (−4.02 to −0.35)	(51)	−1.64 (−3.43 to 0.30)	(19)	−2.49 (−4.80 to −1.62)	(7)	0.018	SGA < FSS
8	−1.86 (−3.88 to −0.08)	(55)	−1.56 (−2.85 to −1.19)	(12)	−2.82 (−4.08 to −1.26)	(11)	0.039	SGA < FSS
9	−1.85 (−3.50 to −0.08)	(46)	−1.95 (−3.10 to 0.29)	(18)	−1.97 (−3.96 to −1.26)	(14)	0.254	
10	−2.13 (−4.07 to −0.27)	(46)	−1.96 (−3.17 to 0.13)	(8)	−1.69 (−3.61 to −0.76)	(10)	0.833	

All data are expressed as medians (ranges). CA, chronological age; ISS, idiopathic short stature; FSS, familial short stature; SGA, small for gestational age; SD, standard deviation.

Table 3. Comparisons of percentage of overweight and body mass index SD score among three groups

CA (years)	ISS group (n)		FSS group (n)		SGA group (n)		P value	Multiple comparison
Percentage of overweight (%)								
5	−2.2 (−16.3 to 18.1)	(36)	−1.8 (−6.6 to 24.3)	(11)	−1.6 (−17.1 to 8.7)	(8)	0.52	
6	2.2 (−13.1 to 22.2)	(56)	3.4 (−6.1 to 27.5)	(14)	−6.2 (−19.0 to 9.6)	(13)	0.01	SGA < FSS
7	3.7 (−10.0 to 22.3)	(51)	11.9 (−3.8 to 33.0)	(19)	−0.8 (−7.5 to 6.0)	(7)	< 0.001	SGA, ISS < FSS
8	4.4 (−11.8 to 16.8)	(55)	10.8 (−0.6 to 23.0)	(12)	−0.3 (−8.8 to 8.8)	(11)	< 0.001	SGA < FSS
9	6.8 (−11.9 to 30.5)	(46)	4.8 (−3.9 to 24.4)	(18)	3.8 (−2.8 to 16.7)	(14)	0.387	
10	5.4 (−11.2 to 34.8)	(45)	3.6 (−4.4 to 56.1)	(8)	7.2 (−0.3 to 21.1)	(10)	0.622	
Body mass index SD score								
5	−0.09 (−2.27 to 1.63)	(36)	−0.12 (−0.71 to 2.07)	(11)	−0.14 (−2.20 to 0.93)	(8)	0.527	
6	−0.32 (−1.86 to 1.28)	(56)	0.28 (−0.95 to 2.00)	(14)	−1.16 (−2.68 to 0.28)	(13)	< 0.001	SGA < ISS, FSS
7	−0.41 (−2.20 to 1.22)	(51)	0.22 (−1.31 to 1.66)	(19)	−1.30 (−2.52 to −0.30)	(7)	< 0.001	SGA, ISS < FSS
8	−0.30 (−2.17 to 0.75)	(55)	−0.06 (−1.17 to 0.51)	(12)	−1.31 (−1.72 to −0.02)	(11)	0.003	SGA < ISS, FSS
9	−0.38 (−2.00 to 1.10)	(46)	−0.51 (−1.48 to 1.48)	(18)	−0.84 (−2.06 to 0.00)	(14)	0.117	
10	−0.77 (−2.74 to 0.96)	(46)	−0.81 (−1.88 to 1.52)	(8)	−0.58 (−1.95 to 0.47)	(10)	0.828	

All data are expressed as medians (ranges). CA, chronological age; ISS, idiopathic short stature; FSS, familial short stature; SGA, small for gestational age; SD, standard deviation.

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SGA groups (P < 0.01 for all groups), and the median POW among 7-yr-olds in the FSS group was significantly higher than that in the age-similar ISS group (P < 0.01). The median BMI SD scores among 6-, 7-, and 8-yr-olds in the FSS group were significantly higher than those in age-similar SGA groups (P < 0.01 for all groups), and the median BMI SD score among 7-yr-olds in the FSS group was significantly higher than that in the age-similar ISS group (P < 0.05).

In the ISS group, 26 children (13 males) were observed until puberty onset. The puberty onset in all males and in 12 of 13 females was within the normal range, with one female having delayed puberty. To eliminate the effects of children with constitutional delay of growth and puberty (CDGP) characterized by prepubertal BA delay, 144 radiographic images of 25 children (13 males) with ISS whose puberty onset was within normal limits were analyzed. The median CAs at puberty onset in males and females with ISS and without CDGP were 11.9 (11.0–12.6) and 10.8 (8.0–12.1) yr, respectively. Chronological changes in the mean BA delay in these children are shown in **Fig. 3**. There was a significant difference in the mean BA delay among the CA groups and at the onset of puberty (P < 0.001). The median BA delay among 9-yr-olds was significantly greater than that among 5-, 6-, and 7-yr-olds. Median BA delays were −2.34 (−4.35 to −0.75) and −2.51 (−3.02 to −1.05) yr among 9-yr-old males and females, respectively; −2.13 (−2.16 to −0.22) and −2.47 (−4.61 to −0.46) yr among 10-yr-old males and females, respectively; and −1.79 (−3.66 to −0.29) and −1.52 (−2.62 to −0.50) yr among pubertal males and females, with no significant differences between males and females of similar ages (P = 0.463, P = 0.751, and P = 0.265, respectively).

Discussion

This longitudinal data analysis indicated that the degree of BA delay compared with CA was approximately 1–2.5 yr in prepubertal children with ISS and 0–2.0 yr in prepubertal children born SGA, which are similar findings to those in a previous study that analyzed cross-sectional data (1). However, the degree of BA delay compared with CA was approximately 1 yr in prepubertal children with FSS, unlike previous studies which reported no delay (1, 17).

Prepubertal BA is accelerated in obese children (2–5), presumably due to increased insulin secretion (3). In this study, the median BMI SD scores among 6- and 7-yr-olds in the FSS group exceeded 0, unlike in the other two groups. Heavier weight compared to height might explain the small degree of BA delay in children with FSS compared with children with ISS and born SGA.

The CA with the greatest BA delay was 9 yr, 8 yr, and 7 yr in the ISS, FSS, and SGA groups. Adrenal androgen affects bone maturation in prepubertal children (5–7). It is well known that adrenarche starts early in children born SGA (18), but there have been no reports concerning the timing of adrenarche in children with ISS or FSS. The mechanism of adrenarche onset is not clear; however, it is considered to be triggered by an increase in physical size. Cortisol production is directly related with body size, hence older children tend to have higher cortisol concentrations in the adrenal gland. Increased cortisol concentration in the adrenal gland may suppress 3β-hydroxysteroid dehydrogenase type 2 (3βHSD2) activity, enhancing dehydroepiandrosterone (DHEA) production and inducing adrenarche (19). Adrenarche in children with FSS could have started earlier than that in children with ISS because 6-, 7-, and 8-yr-olds with FSS were heavier than their ISS counterparts. Since adrenarche started late in children with ISS, BA delay

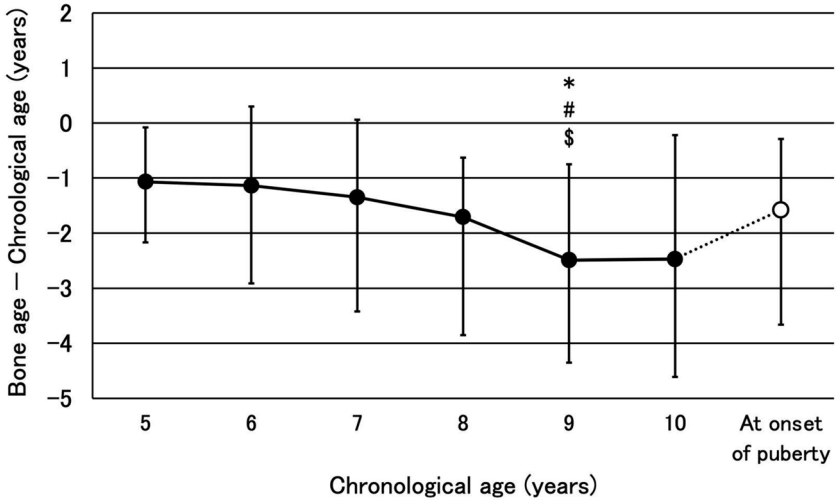

Fig. 3. Chronological change in median (range) bone age delay in 25 idiopathic short stature children without constitutional delay of growth and puberty. There was a statistically significant difference in median bone age delay among chronological age groups (P < 0.001).* P < 0.05, compared with the 5-yr-old group; # P < 0.05, compared with the 6-yr-old group; $ P <0 .05 compared with the 7-yr-old group.

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may have progressed until a CA of 9, unlike in the other two groups. On the other hand, adrenarche in females starts approximately one year earlier than in males. Therefore, a sex-related difference in BA delay in each CA group was examined in children with ISS, which only showed a significant difference in the 6-year-old group.

In the SGA group, the median BA delays were −2.0 to −1.0 yr among 5- to 8-yr-olds, but the median BA delay was −0.04 (range, −2.44 to 0.92) yr among 10-yr-olds (male to female ratio of 1:1). Previous studies reported that in children born SGA with catch-up growth, bone maturation accelerated during prepuberty, and BA at puberty onset was almost equivalent to CA (20, 21). In contrast, a delay of approximately 2 yr in BA compared to CA at puberty onset was observed in children born SGA without catch-up growth (22). In this study, the median height SD scores among children born SGA were −2.47 (range, −3.98 to −2.01) at the first visit and −2.13 (range, −3.40 to −1.61) at the time of the final observation, with a significant difference ($P < 0.001$). Catch-up growth might be a factor indicating that bone maturation was accelerated during prepuberty in children born SGA who were included in this study.

The median value of the IGF-1 SD score at the first visit in children with ISS was as low as −1.04 SD. Low serum IGF-1 levels in children with ISS were considered to be due to low dietary intake and low BMI, compared with children of normal height. In contrast, the mean serum IGF-1 level in children with ISS was significantly lower than that in BMI-matched controls (23). Low serum IGF-1 levels might cause BA delay in children with ISS because IGF-1 promotes bone growth and bone formation (24).

Other factors that increased BA delay in the ISS group were also investigated. In both ISS and FSS groups, there were no significant differences in median height SD scores between initial (−2.32 [range, −3.35 to −1.71] and −2.52 [range, −3.18 to −1.88], respectively) and final (−2.37 [range, −3.48 to −1.54] and −2.45 [range, −2.91 to −1.84], respectively] BA evaluations, and median BMI SD scores at the time of final BA evaluation (−0.55 [range, −2.74 to 1.17] and −0.03 [range, −1.88 to 1.52], respectively) were significantly lower than those at the time of initial BA evaluation (−0.31 [range, −2.17 to 1.63) and −0.04 [range, −1.31 to 2.07], respectively) ($P < 0.01$ and $P < 0.05$, respectively). Since the trend of chronological changes in the physique was the same in the ISS and FSS groups, it was not possible to attribute the increase in BA delay in the ISS group to chronological physical changes. However, the median BMI SD score at the time of the final BA evaluation was significantly lower in the ISS group than in the FSS group ($P = 0.046$); thus, leanness might be one of the reasons for the slow rate of bone maturation in the ISS group.

It is possible that the ISS group included children with CDGP characterized by a prepubertal BA delay. Therefore, chronological changes in BA delay were investigated in children with ISS who had been observed until after the onset of puberty and whose pubertal onset was within the normal range. These children were found to have a BA delay of approximately 2–2.5 yr, from the CA of 8 to the onset of puberty. Although one of the inclusion criteria for CDGP is a BA delay of > 2 yr, it was found that the BA delay in children with ISS without CDGP was approximately similar to that of children with CDGP in this study. Distinguishing children with CDGP from those without CDGP before the onset of puberty using only BA would be challenging. Moreover, although not significant, the degree of BA delay improved at puberty onset compared with that among 9-yr-olds, probably due to the progression of the pubarche.

This study had some limitations. First, the sample sizes in the FSS and SGA groups were small. Second, the relationship between adrenal androgens and bone maturation in children with ISS and FSS was not investigated. In the future, it will be necessary to clarify the relationship between bone maturation and the time of adrenarche by evaluating DHEA sulfate values in prepubertal children with ISS, FSS, and those born SGA.

In conclusion, in prepubertal children aged 8–10 years, the degree of BA delay in the ISS group was greater than that in the FSS and SGA groups. The heavier weight of children with FSS and probable earlier onset of adrenarche in children born SGA compared with children with ISS could have affected prepubertal bone maturation.

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