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PRELIMINARY REPORT

Bone Growth Oscillation: Longitudinal Metabolic Process of Bone Growth in Congenital Adrenal Hyperplasia and Nonendocrine Short Stature

O. Arisaka, H. Kanno, M. Negishi, M. Kojima, K. Nishikura, M. Numata, S. Kanazawa, A. Nitta, T. Kuribayashi, and K. Kano

To clarify the longitudinal metabolic process of bone growth in children, we observed the relationship between the level of serum osteocalcin (OC), a marker of bone metabolism, and growth velocity in 10 prepubertal patients with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency and 9 prepubertal patients with nonendocrine short stature (NESS), but no major hormonal abnormalities influencing bone metabolism. Obserevations were made every 6 months over a 7-year period. In patients with CAH who exhibited a wide variation in growth velocity during the course of the investigation, the levels of OC fluctuated over a wide range, suggesting metabolically variable bone growth. In contrast, in patients with NESS who exhibited a relatively stable growth velocity, the OC level remained within a narrow range, suggesting metabolically stable bone growth. The meaning of such divergent metabolic processes of bone growth observed in CAH and NESS and its relationship to actual bone structure or bone intensity should be further investigated.

NO DOCUMENTED LONGITUDINAL metabolic studies of bone growth in children presenting with endocrine diseases other than primary bone disease or growth hormone (GH) deficiency have been performed.[1] We observed the relationship between actual bone growth and the level of serum osteocalcin (OC), a marker of bone formation,[2,3] in prepubertal patients with congenital adrenal hyperplasia (CAH) and prepubertal patients with nonendocrine short stature (NESS) in a 7-year longitudinal study. The treatment provided for CAH often results in bone growth inhibition during periods of glucocorticoid excess; alternatively, rapid bone maturation as a result of androgen excess can occur if adrenal suppression is inadequate.[4-6] On the other hand, NESS patients do not appear to have any major hormonal abnormalities influencing bone metabolism. We believe that the present longitudinal study, which examined the serial relationship between bone metabolism and growth velocity, is the first of its kind to be reported.

SUBJECTS AND METHODS

Subjects

Ten patients (all girls) with salt-losing CAH due to 21-hydroxylase deficiency and 9 patients (3 girls and 6 boys) with NESS were enrolled in the study. All patients were under the age of 3 years at the time of their enrollment.

A diagnosis of CAH was made based on the presence of virilizing external genitalia and elevated concentrations of plasma 17-hydroxyprogesterone and testosterone during the neonatal period. A salt-wasting state was confirmed by the presence of hyponatremia, hyperkalemia, and an elevated plasma renin level. CAH patients were treated daily with 13 to 38 mg/m^2 of hydrocortisone and 0.025 to 0.1 mg of 9 α-fludrocortisone. The biochemical parameters of all patients were controlled throughout the study as follows: serum electrolytes were entirely normal; concentrations of serum 17 α-hydroxyprogesterone and plasma renin at 9 to 11 AM were below 20 ng/mL (68 nmol/L) and below 10 ng/mL/h (10 μg/L/h), respectively; plasma testosterone concentrations were 18 to 150 ng/dL (0.62 to 5.2 nmol/L).

Patients with NESS were selected during regular physical examinations of healthy 3-year-old children; an endocrinologic diagnosis of NESS was established after following the patients' growth for approximately 5 years. NESS was defined as a propotional short stature (less than -1.5 standard deviation [SD] of the normal age-adjusted mean height, a normal response to GH stimulation tests, and a mean GH level of over 5 μg/L during sleep.[7]

From the Department of Pediatrics, Dokkyo University School of Medicine, Mibu, Tochigi, Japan.
Submitted December 20, 2001; accepted June 18, 2002.
Address reprint requests to O. Arisaka, MD, Department of Pediatrics, Dokkyo University School of Medicine, Mibu, Tochigi 321-0293, Japan.

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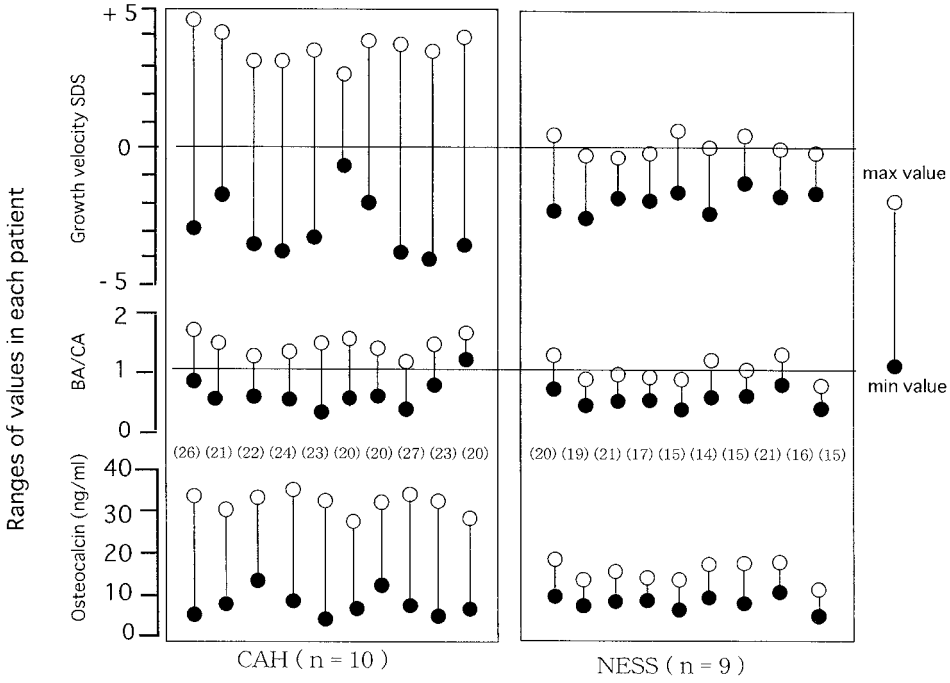

Fig 1. Ranges of maximum and minimum values of growth velocity SD scores, BA/CA ratios, and serum osteocalcin levels in patients with CAH and NESS over a 7-year period. Numbers in parentheses indicate frequency of osteocalcin measurements, (○) maximum value, and (●) minimum value.

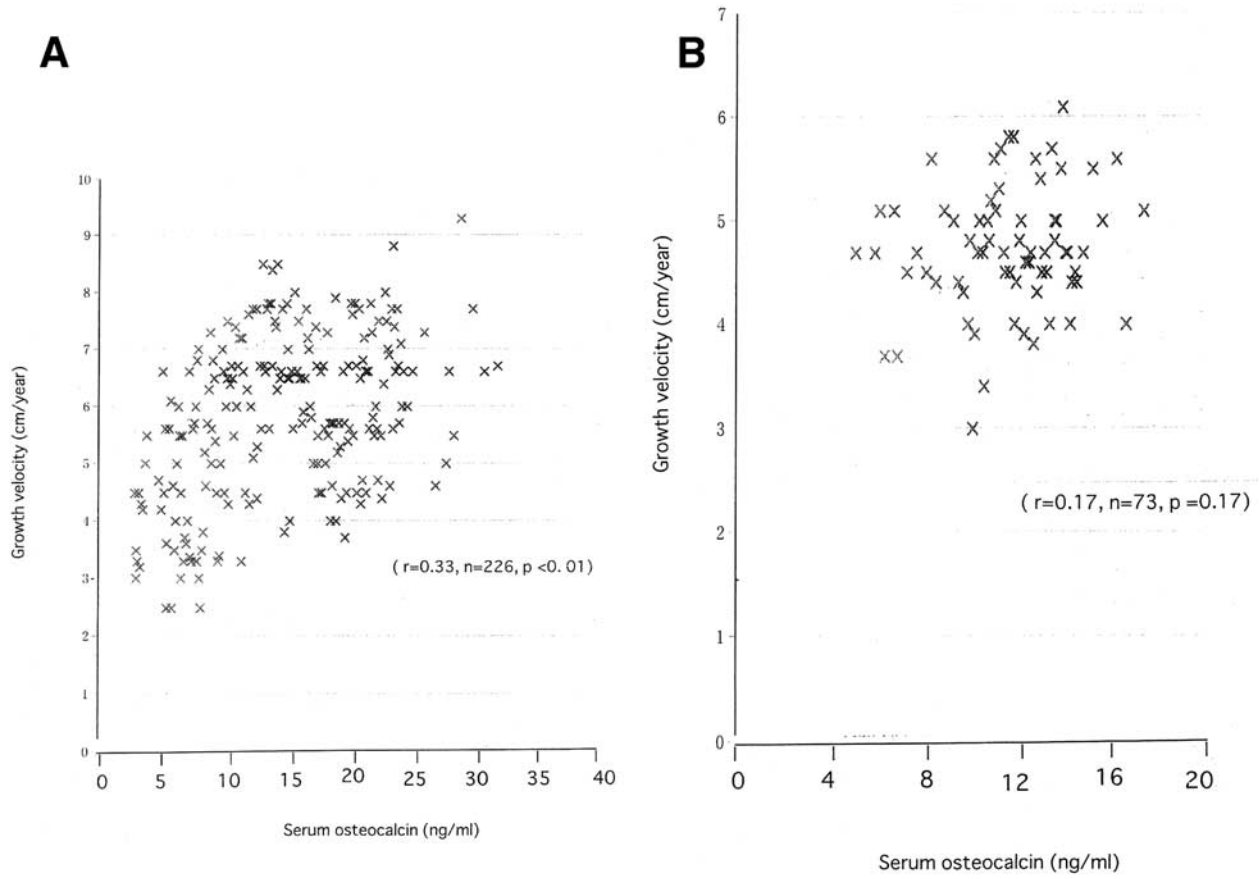

Fig 2. The correlation between serum OC levels and growth velocity in patients with (A) CAH and (B) NESS.

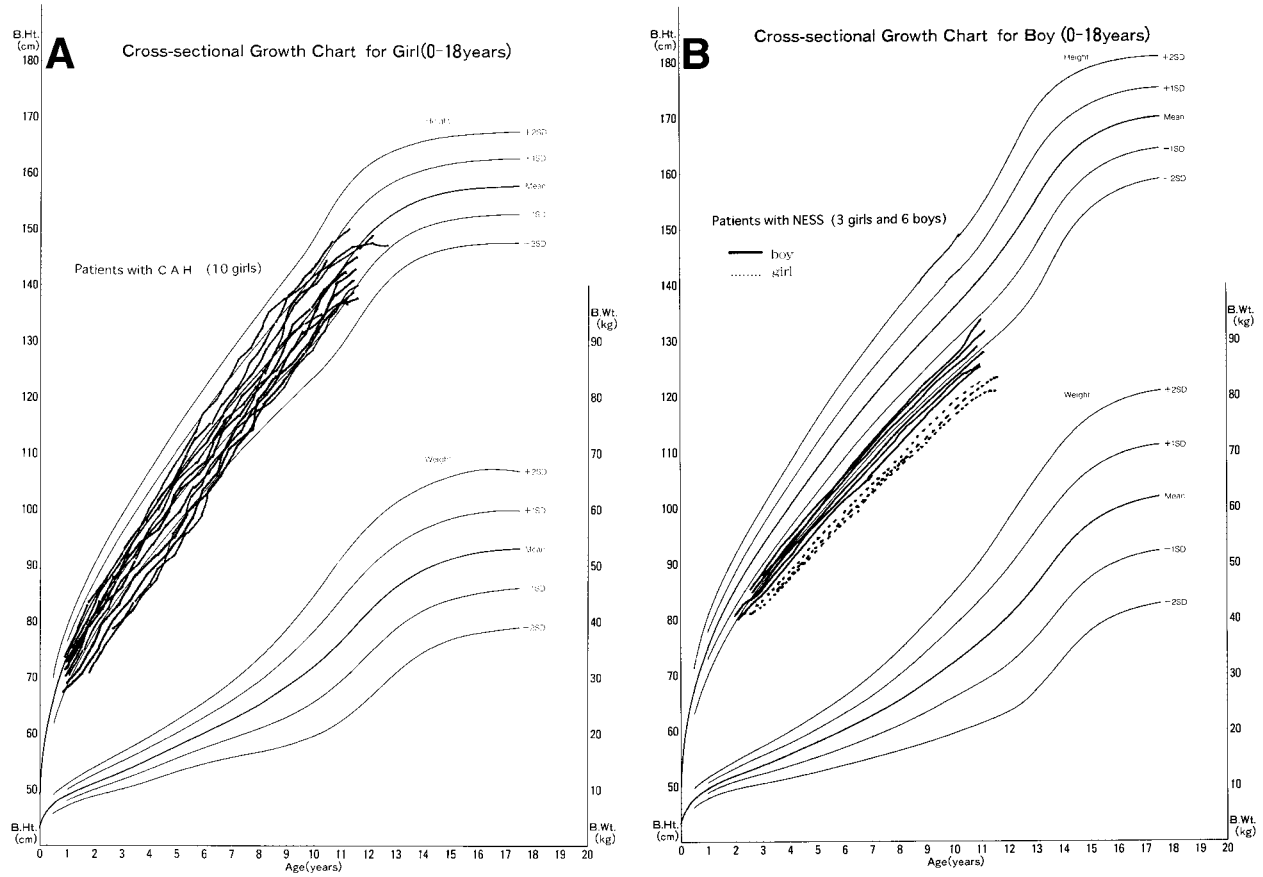

Fig 3. Actual growth curves of the patients with (A) CAH and (B) NESS.

Methods

Standard auxologic assessment and venous sampling were performed every 6 months over a 7-year prospective period. Auxologic assessment included the assessment of signs of androgen and glucocorticoid excess and the measurement of standing height and body weight. Growth velocity was calculated at 6-month intervals and expressed as both the actual growth velocity (cm/year) and the standard deviation score (SDS) for chronologic age.

Bone age was assessed at intervals of 6 months using Tanner Whitehouse-2 (RUS) methods, and the bone age/chronologic age (BA/CA) ratio was calculated. None of the patients developed puberty during the study period.

Blood samples were taken between 10 AM and noon, and the serum was stored at -20°C until assayed. The serum concentration of OC was determined using a radioimmunoassay[8]; the assay was completed within 7 days after the blood sampling. The antiserum used was raised in rabbits immunized with purified intact calf OC and tracer. The standards and samples were analyzed in duplicate. The sensitivity of the assay was 0.44 ng/mL (0.07 nmol/L), and the intra- and interaasay coefficients of variation were less than 5% and 10%, respectively. The mean serum OC concentration in 78 normal prepubertal girls was 12.4 ± 2.5 ng/mL (1.9 ± 0.4 nmol/L) (mean ± SD).

The correlations between serum OC value and growth velocity during the previous 6 months were calculated using linear regression analysis. An unpaired Student's *t* test was used to analyze the significance of difference at a probability level of $P < .05$.

This study was reviewed and approved by a human subjects review board of our hospital. Informed consent was obtained from the patients' parents.

RESULTS

In 10 patients with CAH who exhibited a wide variation in their growth velocity SDS and BA/CA ratio during the course of the investigation, the serum OC levels were also distributed over a wide range (Fig 1). The correlation between serum OC levels and growth velocity in CAH patients was 0.33 (linear regression analysis, $P < .01$, total of 226 measurements). In contrast, the correlation ratio of OC with growth velocity in 9 patients with NESS was 0.11 ($P = .17$, total of 73 measurements) (Fig 2). Actual growth curves of the patients with CAH and NESS are shown in Fig 3.

DISCUSSION

The present longitudinal study shows that the metabolic process of bone growth is variable in patients with CAH; OC levels fluctuated over a wide range and were associated with a wide variation in growth velocity, indicating metabolically variable bone growth. The weak positive correlation between serum OC levels and growth velocity seems to indicate that the bone growth is associated with a change in OC production. In contrast, the smaller changes in OC levels observed in patients

with NESS and associatied with a stable growth velocity indicate metabolically stable bone growth.

Although it has been demonstrated that bone mineral density analyzed by dual-energy x-ray absorptiometry in CAH patients is not decreased, the actual bone intensity is not known.[9-11] The pathogenesis of osteoporosis is dependent not only on bone mineral density, but also on the microarchitectural nature of bone.

In growing bone, bone formation is thought to be affected by an excess of glucocorticoids or androgens. The frequent alterations in hormonal status, ranging from oversuppression to undersuppression of the adrenal glands, which occur during corticosteroid treatment, may produce oscillations in bone growth and bone metabolism that might be deleterious to growing bone.[4,12-14] The meaning of such divergent metabolic processes of bone growth oberved in CAH and NESS is not known. The relationship between alterations in longitudinal bone metabolism and bone quality requires further investigation.

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