**Original Article**

# Adrenal suppression and anthropometric data at two years of age was not influenced by the initial hydrocortisone dose in patients with 21-hydroxylase deficiency

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**Abstract.** In contrast to the glucocorticoid maintenance therapy employed in patients with 21 hydroxylase deficiency (21OHD), the initial therapy remains to be optimized. The Japanese Society for Pediatric Endocrinology recommends a hydrocortisone (HC) dose of 25–100 mg/m$^2$, which is higher than that employed in Western countries. Herein, we aimed to retrospectively verify the impact of initial HC treatment during infancy and early childhood. Between 2010 and 2018, 15 classical patients with 21OHD were enrolled and divided into the following groups based on initial HC therapy: high dose group (HDG, n = 6), medium dose group (MDG, n = 5), and low dose group (LDG, n = 4). In the HDG and MDG, HC was initiated at 100 mg/m$^2$ and reduced to maintenance doses over 4–6 mo and 2–3 wk, respectively. In the LDG, HC was initiated with a maintenance dose of 7 mg/d, accompanied by fludrocortisone and oral NaCl. During the second year, 17α-hydroxyprogesterone was sufficiently suppressed in all three groups. At two years of age, no significant differences in anthropometric data were observed. Our retrospective study did not reveal any apparent advantages or disadvantages of high-dose initial HC therapy for 21OHD, and a lower dose would be preferable for the initial 21OHD treatment.

**Key words:** 21-hydroxylase deficiency, initial therapy, hydrocortisone dose

## Introduction

In Japan, since the introduction of newborn screening for congenital adrenal hyperplasia in 1989, most patients with 21-hydroxylase deficiency (21OHD) have been treated with glucocorticoid from the neonatal period (1, 2). Although early initiation of glucocorticoid therapy from the neonatal period remarkably improved the outcomes of final height, the average final height in 21OHD patients is below the standard height observed in normal healthy adults by approximately –1 standard deviation (SD) (3, 4), and optimization of glucocorticoid therapy remains challenging (5–7, 8). Glucocorticoids have a strong potential for reducing linear growth, whereas undertreatment with glucocorticoids leads to androgen excess, precipitating pubertal development (5–7).

Recent studies have revealed that the final height positively correlates with height at two years of age (9), and the lowest possible hydrocortisone (HC) dose for maintenance treatment during the first two years of life considered crucial for maximizing the final height of 21OHD patients. For maintenance therapy, 15–25 mg/m$^2$ HC therapy is widely accepted (10).

In contrast to maintenance HC therapy, the optimal HC dose for initial treatment has not been established. The consensus statement on 21OHD by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology (ESPE) suggests an HC dose of up to 25 mg/m$^2$ for treatment initiation (11). Conversely, the Japanese Society for Pediatric Endocrinology (JSPE) recommended a considerably higher HC dose of HC (100–200 mg/m$^2$) for the initial treatment (12), and in the revised guideline published in 2014, the recommended dose was lowered to 25–100 mg/m$^2$, which is still higher than that recommended by the ESPE (13). A high initial HC dose may help normalize the elevated adrenal androgen levels during the neonatal

and early infantile periods, followed by sufficient control by a lower maintenance dose.

Our previous study has revealed that the height at two years of age in patients with 21OHD treated with a higher HC dose during initial therapy could be compared with those receiving lower HC doses (14). However, detailed differences between patients with 21OHD treated with higher and lower doses during initial HC therapy have not been assessed. In the present study, we aimed to evaluate the effects of initial HC treatments on clinical profiles during infancy and early childhood in patients with 21OHD.

## Material and Methods

The present study was approved by the ethical board of our institute (M2016-193). Between 2010 and 2018, 15 classical 21OHD patients were introduced HC therapy at our institute (**Table 1**). All subjects revealed positive results on the neonatal screening. For all patients, diagnoses were confirmed endocrinologically and genetically. During this period, we altered the initial HC therapy regimen twice, and the HC dose was reduced from high, 100 mg/m$^2$, to low, 30 mg/m$^2$. None of the 15 enrolled patients exhibited severe adrenal crisis, such as hypotension and potentially fatal arrhythmias, on arrival at our hospital, and the therapy was initiated immediately inpatient. After discharge, all subjects were followed up regularly for at least two years.

Based on the therapeutic regimen, we divided the patients into three groups: high dose group (HDG), medium dose group (MDG), and low dose group (LDG). In the HDG (n = 6, born from April 2010 to March 2012), 100 mg/m$^2$ HC was administered as the initial therapy, and the dosage was gradually decreased to a maintenance dose of 8 mg/d (approximately 25 mg/

**Table 1.** Clinical profiles of subjects

| Patient No. | Tx. group | Sex | GA (W) | BW (g) | Tx from (days of life) | 17αOHP (ng/mL) | Na (mEq/L) | K (mEq/L) |
|---|---|---|---|---|---|---|---|---|
| 1 | high | F | 39 | 4,174 | 11 | 144 | 132 | 6.1 |
| 2 | | M | 36 | 2,770 | 13 | 85.6 | 134 | 5.3 |
| 3 | | F | 37 | 2,910 | 8 | 104 | 138 | 5.4 |
| 4 | | M | 40 | 3,786 | 23 | 174 | 131 | 6.1 |
| 5 | | M | 41 | 3,752 | 7 | 191 | 135 | 5.9 |
| 6 | | F | 37 | 2,704 | 26 | 72.8 | 139 | 5.3 |
| 7 | Medium | M | 40 | 3,316 | 8 | 248 | 132 | 6.7 |
| 8 | | F | 40 | 3,730 | 7 | 263 | 130 | 6.8 |
| 9 | | F | 39 | 3,428 | 6 | 124 | 132 | 5.3 |
| 10 | | M | 39 | 3,046 | 10 | 370 | 125 | 6.3 |
| 11 | | M | 40 | 3,314 | 7 | 89.3 | 141 | 5.5 |
| 12 | Low | M | 38 | 3,032 | 12 | 212 | 132 | 6.3 |
| 13 | | M | 38 | 2,650 | 9 | 265 | 132 | 6.8 |
| 14 | | M | 41 | 3,434 | 7 | 144 | 136 | 5.3 |
| 15 | | F | 39 | 3,126 | 8 | 68.1 | 136 | 5.1 |

| Patient No. | Genotype | Type of 21OHD (SW or SV) | Fludrocortisone (mg/day)* | Oral NaCl supplementation (g/day)* | days of hospitalization |
|---|---|---|---|---|---|
| 1 | Chimera /p.I173N | SW | N.P. | N.P. | 25 |
| 2 | p.R484fs/p.R484fs | SV | N.P. | N.P. | 30 |
| 3 | I2G/p.R484fs | SW | N.P. | N.P. | 24 |
| 4 | Chimera/I173N | SW | N.P. | N.P. | 37 |
| 5 | E6 Cluster/p.R357W | SW | N.P. | N.P. | 37 |
| 6 | p.I173N/p.R357W | SV | N.P. | N.P. | 28 |
| 7 | Chimera/Chimera | SW | N.P. | N.P. | 21 |
| 8 | I2G/p.R484fs | SW | N.P. | N.P. | 22 |
| 9 | Chimera/p.I173N | SW | N.P. | N.P. | 18 |
| 10 | I2G/Del | SW | N.P. | 0.9 | 26 |
| 11 | p.I173N/p.R355C | SW | N.P. | 1 | 26 |
| 12 | I2G/c.940-1G>C | SW | 0.05 | 1 | 14 |
| 13 | Chimera/I2G | SW | 0.05 | 1 | 18 |
| 14 | Chimera/Del | SV | 0.05 | 0.8 | 36** |
| 15 | p.I173N/p.R484fs | SV | 0.05 | 0.8 | 11 |

Tx, treatment; GA, gestational age; BW, birth weight; 17αOHP, 17α-hydroxyprogesterone; 21OHD, 21 hydroxylase deficiency; SW, salt wasting; SV, simple virilizing; N.P., not prescribed. * Treatment with glucocorticoid therapy simultaneously. **: Not included in the statistical analysis because the hospitalization was prolonged due to laryngomalacia.

m2) over 4–6 mo. In the MDG (n = 5, born from April 2014 to March 2016), 100 mg/m² HC was administered, as in the HDG but was reduced more promptly to the maintenance dose of 7–8 mg/d in 2–3 wk. In the LDG (n = 4, born from April 2016 to March 2018), patients were treated with 7 mg/d (approximately 30 mg/m² during the neonatal period), which was nearly equivalent to maintenance therapy, and the therapy was shifted to maintenance therapy without changing the dose (**Fig. 1**). In the HDG and MDG, fludrocortisone (0.05–0.1 mg/d) and oral NaCl supplementation were introduced when the HC dose was decreased to < 50 mg/m². In the LDG, fludrocortisone (0.05 mg/d) and oral NaCl supplementation were initiated simultaneously with HC therapy (**Fig. 1**, **Table 1**). For screening undertreatment of the initial therapy, we closely monitored the general condition, serum sodium and potassium levels, and body weight gain during the first month of life. The patients in HDG and MDG were treated inpatients when more than 12 mg/d (approximately 50 mg/m²/d) of HC was administrated. The patients in the LDG were initially treated inpatient, and when continuous body weight gain more than 5–7 d was documented, the treatment was shifted to outpatient.

During the follow-up period, we examined the subjects every 1–3 mo. No signs or symptoms of undertreatment, such as failure to thrive, electrolyte abnormalities, and excessive adrenal androgen levels, were observed in any subjects. We retrospectively analyzed clinical data during the first 2–4 yr of life, including anthropometric measurements (height, Δheight, body weight, Δbody weight, body mass index [BMI] SD score), endocrinological data from random blood specimens (17α-hydroxyprogesterone [17αOHP], dehydroepiandrosterone sulfate [DHEAS] DHEAS), the frequency of severe adrenal insufficiency and social factors, i.e., the length of initial hospital stay. The anthropometric data at two years of age were represented by data obtained from 1 yr 10 mo to 2 yr 2 mo. ΔHeight and Δweight indicate the gain in height and body weight from one to two years of age, respectively. The definition of severe adrenal crisis was the condition that could be life threatening, such as hypotension, prolonged seizure, hypoglycemia less than 45 mg/dL of blood sugar, severe hyponatremia less than 125 mEq/L and severe hyperkalemia more than 7 mEq/L.

### Statistical analysis

The SD values of height, body weight, and BMI were calculated according to the anthropometric data of Japanese children from the JSPE (15). For statistical analysis, we employed a one-way analysis of variance.

### Results

At the introduction of HC therapy, there were no statistically significant differences in the gestational age, birth weight, serum levels of 17αOHP, Na and K, and
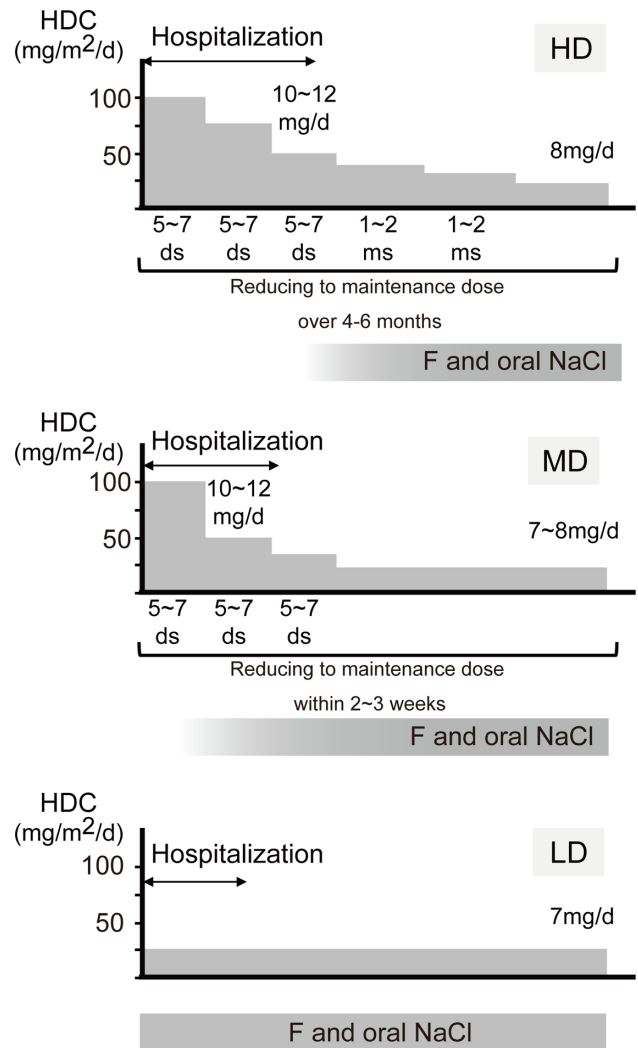


**Fig. 1.** Diagrams of the three protocols for the glucocorticoid initiation therapy. HC, hydrocortisone; HD, high dose; MD, medium dose; LD, low dose; F, fludrocortisone.

the days of life among the three groups (**Table 2**). No cases in the LDG revealed severe adrenal crisis on the first visit to our hospital, not requiring a stress dose of HC for the initial therapy. During the first two years of life, no patients required increased HC for maintenance.

Compared to the HDG, the serum level of 17αOHP remained relatively high in the MDG and the LDG (**Fig. 2**), and the age when the 17αOHP level was less than 10 ng/mL sequentially twice or more was significantly different (**Table 3**). On the other hand, on and after one year of life, the serum levels of 17αOHP were sufficiently suppressed in all three groups (**Fig. 2**). Another adrenal androgen marker, DHEAS, had similar tendencies, but no statistical significance among the HD, MD and LDG at the age of two years was documented (**Table 3**).

Among the three groups, we did not observe any significant differences in anthropometric data, body height and body weight change SDs, BMI SDs, body height and body weight, at the age of two (**Fig. 3**, **Table 3**).

**Table 2.** Clinical profiles of each group

| Tx. group | GA | BW | Tx from (days of life) | 17αOHP (ng/mL) | Na (mEq/L) | K (mEq/L) |
|---|---|---|---|---|---|---|
| HDG (ave ± SD) | 38.3 ± 1.8 | 3,349 ± 574 | 14.7 ± 7.3 | 128.6 ± 7.3 | 134.8 ± 2.9 | 5.7 ± 0.4 |
| MDG (ave ± SD) | 39.4 ± 0.5 | 3,366 ± 220 | 7.6 ± 1.4 | 218.9 ± 101.4 | 132.0 ± 5.2 | 6.1 ± 0.6 |
| LDG (ave ± SD) | 39.0 ± 1.2 | 3,060 ± 280 | 9.0 ± 1.9 | 172.2 ± 73.9 | 134.0 ± 2.0 | 5.9 ± 0.7 |
| *p* value | 0.504 | 0.557 | 0.106 | 0.248 | 0.528 | 0.527 |

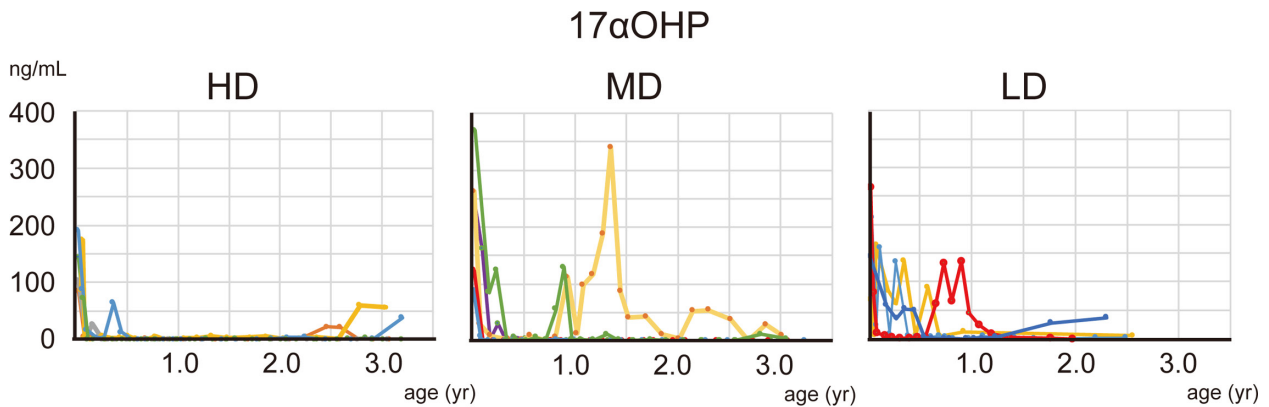Tx, treatment; GA, gestational age; BW, birth weight; 17αOHP, 17α-hydroxyprogesterone.



**Fig. 2.** Chronological changes of the serum 17αOHP levels in the subjects. HD, high dose; MD, medium dose; LD, low dose.

**Table 3.** Clinical outcomes of each group

| | Days of life at 17αOHP <10 ng/mL | Days of life at DHEAS <80 ng/mL | Ht SDs at 2 yr | ΔHt SDs (0–1 yr) | BW SDs at 2 yr | ΔBW SDs (0–1 yr) | BMI SDs at 2 yr | Length of stay (d) | Episodes of severe adrenal crisis |
|---|---|---|---|---|---|---|---|---|---|
| HDG (Ave ± SD) | 49 ± 27 | 32.1 ± 7.4 | −1.13 ± 0.65 | −1.84 ± 1.1 | −0.4 ± 0.91 | −0.75 ± 1.5 | 0.65 ± 0.75 | 30.0 ± 5.2 | 0 |
| MDG (Ave ± SD) | 310 ± 450 | 24.3 ± 9.1 | −1.16 ± 1.25 | −1.85 ± 1.7 | −0.25 ± 1.26 | −1.35 ± 1.1 | 1.12 ± 1.28 | 22.6 ± 3.1 | 0 |
| LDG (Ave ± SD) | 271 ± 156 | 96.5 ± 92.0 | −0.10 ± 1.25 | −0.76 ± 0.9 | 0.47 ± 0.80 | −0.29 ± 1.2 | 0.87 ± 0.22 | 14.3 ± 2.9 | 0 |
| *p* | <0.05 | 0.168 | 0.27 | 0.40 | 0.38 | 0.49 | 0.41 | <0.05 | - |

DHEAS, dehydroepiandrosterone sulfate; Ht, height; BW, body weight; BMI, body mass index.

The length of hospitalization was significantly shorter in the LDG than that in the MDG and the HDG (**Table 3**). The frequency of the adrenal crisis was not significantly different among the three groups over the first two years of life.

## Discussion

Consistent with our previous study (14), the current study suggested that the HC dose for the initial treatment did not affect growth in 21OHD patients during the first two years of life. Furthermore, the growth was not significantly impaired in the HDG, in which high dose of HC was extended to first 4–6 mo of life. The data suggested that the negative glucocorticoid effects on growth during the first 3–4 mo after birth was limited. Indeed, in the previous report which showed that, during early childhood, the growth at the age of 6 to 12 mo, rather than during the first 6 mo of life, was highly susceptible to glucocorticoid excess (16). In addition to

growth, we did not identify any significant effects for obese parameters, such as BMI and Δbody weight in HDG, suggesting that a high dose of HC during the early infantile period has limited impacts for obesity during childhood.

The serum level of 17αOHP in the LDG was not sufficiently suppressed during the first year of life. Whereas, in the second year, the 17αOHP level decreased to a level comparable to that of the HDG. A similar transitional pattern in the serum level of another adrenal androgen, DHEAS, was observed. Our data suggest that a lower dose of initial treatment sufficiently suppressed the adrenal androgen level in the second year of life.

For the initial therapy of 21OHD, appropriate management for salt wasting is essential. In contrast to the higher dose of HC therapy, a lower dose of HC with low sodium administration is not capable of improving salt wasting, and additional treatment for salt wasting is required. In addition to fludrocortisone, For low-dose HC treatment, oral NaCl should be accompanied with
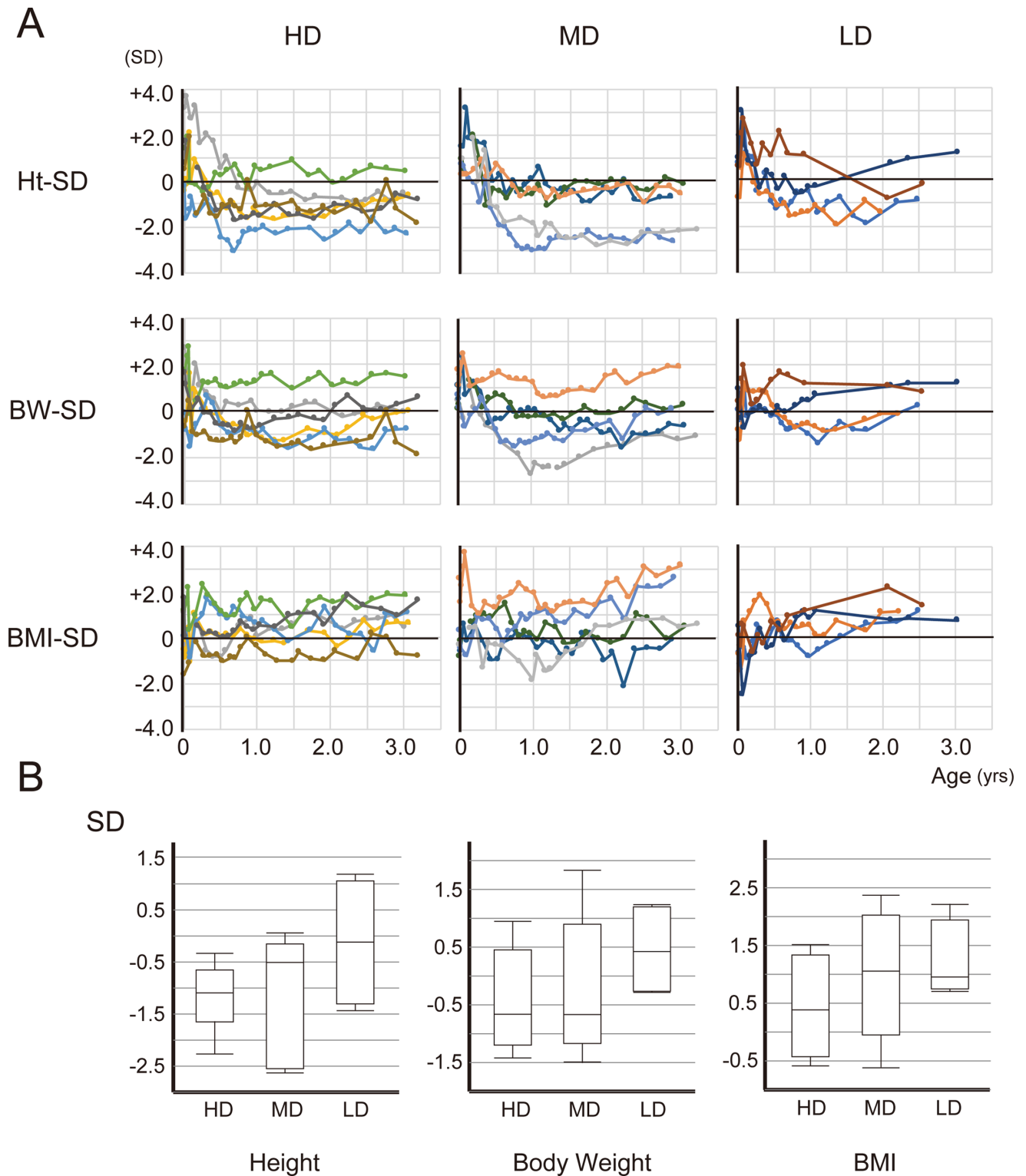
**Fig. 3.** A: Chronological changes of the SD score of anthropometric parameters, height (Ht), body weight (BW) and body mass index (BMI) in each subject. B: Box-and-whisker plot of the SD values of anthropometric parameters, height (Ht), body weight (BW) and body mass index (BMI), at the age of two. No significant differences were observed.

fluorocortisone. Sufficient sodium supplementation is essential for salt wasting, because sodium expands the extracellular volume and the delivery of $Na^+$ to the distal collecting tubules create a favorable gradient for $K^+$ excretion (17, 18). The potency of the treatment is determined by the additive effect of fluorocortisone and NaCl intake, and the dosage of fluorocortisone may change according to the amount of NaCl intake. Indeed, in the condition of aldosterone resistance, pseudohypoaldosteronism, a sole treatment of high Na intake efficiently improves hyponatremia and hyperkalemia (19).

In our study, we used body weight gain as the major biomarker to evaluate the effects of the HC therapy. The existence of glucocorticoid insufficiency or salt-wasting causes body weight loss, and appropriate body weight gain indicates that glucocorticoid insufficiency and salt wasting are properly managed. Indeed, none of our patients with appropriate body weight gain developed hyponatremia, hyperkalemia and other clinical symptoms or signs indicating adrenal insufficiency. A recent report of newborns screening in Tokyo revealed that body weight loss is an excellent predictor for the diagnosis of 21OHD and the development of salt wasting (20).

Our present study has several limitations. First, our cohort was extremely small, and we cannot exclude the possibility that no significant difference in anthropometric data at the age of two years was due to the cohort size rather than the unresponsiveness of growth to the initial HC treatment. However, we think such a possibility is low, because our previous report is also consistent with our speculation (14). To clarify the issue, further accumulation of the cases is required. Second, we evaluated the level of 17αOHP, which has a circadian rhythm, using randomly obtained samples. This could have resulted in inaccurate estimations.

However, the levels of 17αOHP in all the three groups were suppressed during their second year of life when the adrenal circadian rhythm is not established, and we speculate that the influence of the random sampling would be limited. Consistently, the levels of DHEAS which has no apparent circadian rhythm due to its long half-life, revealed a similar tendency to that of 17αOHP. Urine pregnanetriol is an excellent marker that directly reflects the levels of 17αOHP, but it has not been measured regularly in several subjects in our cohort. Third, we did not include episodes of mild adrenal crisis for our analysis, because detailed analysis of milder adrenal crisis requires precise medical records which were not available in our retrospective analysis.

In summary, our retrospective study did not reveal any apparent advantage or disadvantage in using a higher dose of initial HC therapy for 21OHD. Currently, the lower dose regimen is accepted worldwide for the initial treatment of 21OHD. Besides, the shorter hospitalization suggest that lower dose regimen is more efficient in socio-economical aspects. Given the fact, without robust advantages to the clinical outcomes, employing a higher dose regimen would not be supported, and a lower dose of HC treatment would be preferable for the initial 21OHD treatment.

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