Initial high dose hydrocortisone (HDC) treatment for 21-hydroxylase deficiency (21-OHD) does not affect linear growth during the first three years of life

Kei Takasawa, Makoto Ono, Kentaro Miyai, Yohei Matsubara, Fumihiko Takizawa, Toshikazu Onishi, Kenichi Kashimada and Shuki Mizutani

Department of Pediatrics and Developmental Biology, Tokyo Medical and Dental University, Tokyo 113-8510, Japan

Abstract. An initial high-dose treatment of glucocorticoid has been proposed to prevent chronic androgen excess, improving the final height prognosis of 21-hydroxylase deficiency (21-OHD) patients. In Japan, it is recommended to use an extremely high-dose of hydrocortisone (HDC) (100-200 mg/m²/day) for initial treatment by the Japanese Society for Pediatric Endocrinology. However, a precise evaluation of the treatment has not been carried out. In this study, we retrospectively analysed the effects of initial high-dose HDC therapy on the linear growth of classical 21-OHD patients discovered by newborn screening. Thirty patients (14 females) were eligible for this study, all of whom were initiated with high dose HDC therapy. The height standard deviation score (Ht-SDS) was 0.76 ± 0.65 at birth, and decreased to -1SD or less until the age of 12 months, subsequently catching up by 3 years of age (-0.56 ± 0.76). The growth pattern and the height at the age of two years were very similar to those previously observed in patients without initial high dose HDC therapy. We did not find any significant difference in growth retrospectively between the high- or low-dose HDC group (initial treatments of ≥150 mg/m²/day and 100 mg/m²/day, respectively). Bone ages did not exceed chronological ages at the ages of three and six years. Our data suggest that an initial high-dose HDC treatment does not profoundly affect linear growth during first three years of life and that the treatment could be a valuable option for 21-OHD patients without having an obvious adverse effect on linear growth.

Key words: 21-hydroxylase deficiency, Hydrocortisone, Initial high-dose treatment, Linear growth, Newborn screening
Pediatric Endocrinology (JSPE) recommends an even higher dose of HDC (100-200 mg/m²) for initial treatment [10]. In spite of the widely accepted usage of initial therapy in Japan, there are few reports that evaluated the clinical benefit and adverse effects of the initial high dose treatment, and regarding the Japanese protocol, there are no precise studies that support the validity of the initial high dose treatment.

In order to evaluate the validity of high dose HDC initial therapy for linear growth, we retrospectively analysed growth profile during the first three years of life of 30 patients with 21-OHD detected by newborn screening and received a high dose of HDC according to the JSPE protocol. In these patients, the linear growth during the first three years of life was not noticeably less than that in patients in other studies that received low dose glucocorticoid therapy without an initial high dose of HDC. Our data suggest that high dose glucocorticoid treatment might be a valuable option for the initial therapy of 21-OHD.

**Material and Methods**

In Japan, newborn screening for 21-OHD has been performed since January, 1989 [10-12]. Between 1989 and 2011, we followed thirty classical 21-OHD patients who were detected by newborn screening for at least three years. The patients were provisionally classified into the two forms of salt-wasting (SW) and simple virilising (SV) according to plasma sodium and potassium levels at diagnosis. The number of the patients of each phenotype was showed in Table 1. Treatment for all patients was introduced in the neonatal period and patients with nonclassical forms of 21-OHD were not included in this study. The estimated target height from the parent’s height [male (n=10) 170 ± 3.8 cm, female (n=7) 159 ± 4.3 cm] was not different from healthy Japanese adult heights. All patients were examined and followed up in our hospital until the age of 3 years.

Initially all 30 patients were administrated with 100-200 mg/m²/day of HDC, and the dosage of HDC was decreased gradually to the maintenance dose (20-40 mg/m²) by 2-3 months after birth based on the clinical guidelines for 21-OHD in Japan (Table 2). During decreasing the dosage of HDC, some patients initially diagnosed as having SV type, showed signs of salt wasting, such as poor weight gain or hyponatremia, and we initiated fludrocortisone for ten SV patients, and for eight SV patients, sodium chloride supplementation was appended. The dosage of the medicine was mainly adjusted based on surface of body area with considering auxological and endocrinological data.

### Table 1 Physical profiles of SW and SV 21-OHD patients at birth and laboratory data at diagnosis

<table>
<thead>
<tr>
<th>21-OHD type</th>
<th>At birth</th>
<th>At diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gestational age (week)</td>
<td>Body weight (g)</td>
</tr>
<tr>
<td>SW Male: 11, Female 7</td>
<td>39 ± 1.5</td>
<td>3136 ± 325</td>
</tr>
<tr>
<td>SV Male: 5, Female: 7</td>
<td>39 ± 0.8</td>
<td>3281 ± 220</td>
</tr>
<tr>
<td>Total Male:16, Female: 14</td>
<td>39 ± 1.2</td>
<td>3186 ± 292</td>
</tr>
</tbody>
</table>

Values indicate mean ± SD.

a, SW (salt-wasting form) characterized by Na<130 mEq/L and/or K>6 mEq/L at diagnosis; *, p<0.05

### Table 2 Clinical guidelines of the Japanese Society for Pediatric Endocrinology (JSPE) for treating 21-OHD patients with HDC

<table>
<thead>
<tr>
<th>Therapy type</th>
<th>Age</th>
<th>HDC dose (mg/m²/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>Neonates</td>
<td>100-200³,c</td>
</tr>
<tr>
<td></td>
<td>Infancy</td>
<td>20-40</td>
</tr>
<tr>
<td>Maintenance</td>
<td>Early childhood</td>
<td>15-30</td>
</tr>
<tr>
<td></td>
<td>School age</td>
<td>15-25</td>
</tr>
</tbody>
</table>

a, Combination therapy with fludrocortisone acetate and NaCl could be considerable according to symptoms; b, Divided into 3 doses; c, Tapering every 5-7 days; Shift to maintenance therapy 3-4 weeks later; d, Adjust the dosage by monitoring clinical data (Na, K, 17OHP(<30nmol/L), ACTH, PRA(0.5-5 ng/mL/h))
Results

The clinical profiles of the patients are showed in Table 1. All patients were born at full term and the mean ± SD of birth weight was 3186 ± 292 g. The birth Ht-SDS standardised to gestational age was 0.76 ± 0.65, which was higher than normal neonates as previously reported [15, 16]. The average genetic target heights estimated from the parents’ heights was 170 ± 3.8 cm in boys and 159 ± 4.3 cm in girls, which was not significantly different from those of healthy adult Japanese [17]. The mean value of 17-hydroxyprogesterone (17-OHP) at diagnosis was 584 nmol/L (193 ng/mL), and the HDC therapy was started during neonatal period (12.5 ± 5.4 days after birth).

The course of HDC treatment in each group is shown in Table 3. Patients were treated according to the JSPE guidelines (Table 2). On the initial treatment, the dosage of HDC in SV group was 100 mg/m² and was significantly lower than that of the SW group which were treated with 100-200 mg/m² of HDC. The maintenance therapies of the SV and SW groups were not significantly different.

The male and female patients showed similar changes of Ht-SDS with time: Ht-SDS was higher than that of normal neonates at birth, decreased to -1SD or less by the age of 12 months, and subsequently rose until 3 years of age (Fig. 1A). The significant difference of Ht-SDS between male and female were not observed during the first three years of life, and the growth pattern observed in this study was similar to the previous report on which the initial high dose HDC therapy was not performed [8]. The heights at the age of two years (boys: -0.59SD ± 0.99, girls: -1.00SD ± 0.96, Fig. 1A) were similar to those of patients that did not receive initial high dose HDC therapy (-0.6SD ± 0.9 and -0.9SD ± 1.2, respectively) [8]. In other words, initial high dose HDC treatment did not appear to have any significant effect on height at the age of two years.

For more precise evaluation of the relationship between initial dose of HDC and the Ht-SDS during

<table>
<thead>
<tr>
<th>21-OHD type</th>
<th>SW</th>
<th>SV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>178±71</td>
<td>100±0*</td>
</tr>
<tr>
<td>3</td>
<td>41.9±5.9</td>
<td>40.0±3.7</td>
</tr>
<tr>
<td>6</td>
<td>34.9±5.8</td>
<td>31.3±3.7</td>
</tr>
<tr>
<td>9</td>
<td>30.6±5.6</td>
<td>27.4±4.1</td>
</tr>
<tr>
<td>12</td>
<td>30.4±4.9</td>
<td>25.1±3.8</td>
</tr>
<tr>
<td>24</td>
<td>21.2±3.8</td>
<td>18.6±2.5</td>
</tr>
<tr>
<td>36</td>
<td>17.8±2.8</td>
<td>16.9±2.0</td>
</tr>
<tr>
<td>Mean</td>
<td>147±53</td>
<td>41.1±3.8</td>
</tr>
</tbody>
</table>

Values indicate mean ± SD. *, p<0.05

Fig. 1 Course of height standard deviation score (Ht-SDS) (A), male and female 21-OHD patients (B), low dose (LD) and high dose (HD) groups (C), patients with the SV and SW forms. The symbols are identified in the graph. Error bars indicate mean ± SEM. **, p<0.005; *, p<0.05.
It is reported that the dosage of glucocorticoid had significant negative effects on linear growth between the age of 6 and 12 months [7]. The findings that final height of 21-OHD patients was positively correlated with the height at the age of two years [6], allowed us to evaluate the potential long-term adverse effects for growth by high dose initial HDC treatment by analysing linear growth in the first three years of life, especially at the age of two years.

To evaluate the effect of the severity of the neonatal period, we compared the Ht-SDS for the SW and SV patients that were provisionally classified during neonatal period. At the age of 6 and 12 months, the Ht-SDS of SW was significantly lower than that of the SV form, however, at the ages of 2 and 3 years of age, there were no significant differences between the two groups (Fig. 1C).

In order to estimate the androgen excess, we examined bone age (BA) of the patients. During the first one or three years of life, bone age is not accelerated by androgen effect [18, 19], and we chose the chronological age (CA) of three and six years for BA examination. At the age of three years, BA was mildly delayed (boys: BA/CA was 0.75 ± 0.17 in males and 0.79 ± 0.08 in females) (Fig. 2). The ratios were not significantly different between the sexes. At the age of six years, the BA/CA ratios were slightly higher (0.91 ± 0.17 and 0.87 ± 0.15, respectively) (Fig. 2) but still less than 1.0. These results suggest that the patients were not exposed to excessive androgen levels during the first six years of life.

**Discussion**

It is reported that the dosage of glucocorticoid had significant negative effects on linear growth between the age of 6 and 12 months [7]. The findings that final height of 21-OHD patients was positively correlated with the height at the age of two years [6], allowed us to evaluate the potential long-term adverse effects for growth by high dose initial HDC treatment by analysing linear growth in the first three years of life, especially at the age of two years.

The present results suggest that initial high dose HDC treatment does not affect the linear growth of 21-OHD patients, at least, in the first three years of life. First, we showed that, at the age of two years, the Ht-SDS of our subjects was very similar to that of subjects who did not receive an initial high dose of HDC [8]. The HDC maintenance dose that we used (16.9-41.9 mg/m$^2$) was higher than that used by Bonfig et al. (9.3-12.8 mg/m$^2$), excluding the possibilities that the difference between the maintenance therapies could affect the recovery of Ht-SDS. Second, we did not observe a significant difference between high and low dose groups during the first two years of life. At the second point, we should consider a limitation of this comparison that the HD and LD groups were not randomized and not matched for severity of the disease or HDC maintenance dose.

![Fig. 2](image_url)  
Fig. 2  Ratios of bone age (RUS) to chronological age at 3 and 6 years of age
We presume that the growth inhibition during early infancy might be caused by not only HDC, but also other factors, such as chronic adrenal insufficiency including salt wasting, therapies other than HDC. Linear growth during the first 6 months of life was found to be decreased even by low doses of HDC (approximately 10 mg/m²/day) [8]. However, the lowest HT-SDS values observed in our study (boys: -1.09SD ± 0.99 at 6 months of age, girls: -1.26SD ± 0.94 at 15 months of age) were not very different from those reported by Bonfig et al. (boys: -0.9SD ± 0.9 at 12 months of age, girls: -1.3SD ± 1.4 at 18 months of age). In addition, a significant difference of Ht-SDS was not observed between high dose and low dose groups, but there was significant difference between SV and SW groups at the 6 and 12 months of age.

Preventing exposure to androgen excess is essential for improving final height, and the initial high dose HDC treatment might help to suppress long-term androgen synthesis. To test this hypothesis, adrenal androgens are not suitable markers because the sensitivity of the assay is not sufficient. Instead, we evaluated bone age at the ages of three and six years as previously reported [8, 20]. The BA/CA ratios of the patients at each age were less than 1.0. The bone ages that we measured at age three years (boys: 2.35 ± 0.60, girls: 2.42 ± 0.28) tended to be lower than those measured by Bonfig et al. (boys: 2.9 ± 0.5, girls: 2.7 ± 0.5) [8]. This suggests that an initial high dose of HDC inhibits bone maturation during infancy and early childhood, and could improve final height.

We should consider some limitations of the study. Firstly, we cannot exclude the possibilities that the difference of the ethnicities might affect the interpretation of the comparison our data to that of Bonfig et al. Secondarily, our study was performed retrospectively, and the objects were not randomized. Thirdly, as well as the data of Bonfig et al., the period we observed was short, the first three years of life. Though we did not find obvious difference of heights between the patients treated with and without fludrocortisone, we should also consider the effect of fludrocortisone for height prognosis as previously reported [5]. For a precise evaluation of the therapy, a future randomized controlled study is necessary.

In summary, we retrospectively analysed the growth profiles of patients with classical 21-OHD that were treated with an initial high dose of HDC during the neonatal period. Growth in the first three years of life was not noticeably different from that of patients in a previous study that were not given an initial high dose of HDC. The bone ages of our subjects did not exceed the chronological ages at the ages of three and six years, suggesting that androgen was sufficiently suppressed in the first three years of life. Our data suggest that treatment with an initial high dose HDC might be beneficial for 21-OHD patients during early childhood without having noticeable adverse effect on linear growth.

Acknowledgements

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References


